GENERAL PATHOLOGY

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mated. Within late years there has been fostered somewhat a tendency toward the disparagement of the writing of text-books as compared to the prosecution of research work, but of the intrinsic worth of a text-book such as the one under consideration there can be no question. Truly, as great a service as that of pure investigation is rendered by the calm and judicious spirit, who, without prejudice, wisely sifts the great mass of collected investigations and brings from them a tangible order and scheme. And upon such a service rests the great reputation of Ziegler's text-book.

ALDRED SCOTT WARTHIN.

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NOTE.—Because of the difference in the size of the page it has been found necessary to reduce slightly some of the illustrations. In such cases the magnification or amplification has been changed to meet the amount of reduction.

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GENERAL PATHOLOGY.

INTRODUCTION.

THE **life** of an organism is revealed only through its vital manifestations and activities. **Physiology**, the science of the normal or healthy life, teaches us concerning these activities. At the same time it shows us that the vital functions are performed according to definite laws having their foundation in the structure of the organism. Changes in this organic structure, *manifesting themselves in vital phenomena differing from those regarded as normal*, form the material basis of **disease** or **abnormal** life. The return to the normal condition is regarded as the sign of **recovery** or **healing**.

A permanent cessation of all vital functions leads to **death**. Temporary interruptions of the vital activities without the loss of the possibility of a return to the normal state may be seen in the condition of **apparent death** or in congelation, which may be followed either by death or by a return to life (anabiosis).

When there are present pathological changes in the tissues, arising either before the appearance of pathological symptoms or persisting after their cessation, so that at any time a new outbreak of the latter may take place, the disease is spoken of as **latent**.

The *entire science of disease* is embraced by **Pathology**. As its first task there falls to it the *determination* of *the causes and origin* of *pathological processes*, these two divisions constituting **etiology** and **pathogenesis**. A second task lies in the investigation of the anatomical changes underlying the pathological alterations of function; and the branch of the science to which this field is assigned is known as **pathological anatomy** or **anatomical pathology**. Since the structure and finer organization of the different tissues vary according to their functions, and as we cannot conceive of vital manifestations without a material substratum for them, it is reasonable to assume that pathological manifestations of life must likewise be the expression of material changes in the tissues concerned. Moreover, experience has taught us that in the case of any pathological alteration of function of any tissue or organ, there may be demonstrated in the latter changes of structure, in part even macroscopically, while at other times they can be made out only with the aid of the microscope and by means of especial histological methods of investigation.

A third field of labor belonging to pathology is concerned with the *observation and interpretation of the symptoms of disease as seen in the patient*, and this branch of general pathology is designated **clinical pathology, pathological physiology, physiological** or **biological pathology.** Its facts are ascertained in part by simple observation and examination of the patient, and in part through the utilization of especial physical and chemical

methods of examination. A successful application of the results obtained by the methods of clinical or biological pathology requires in the first place a **knowledge** of **the pathological-anatomical** changes present, as well as of their **etiology** and **pathogenesis.** As a further help to the interpretation of disease a **knowledge** of the *chemical processes* taking place in the living organism under the influence of the vital activity of the cells and the unformed ferments separable from them is essential. This knowledge is specialized in the science of **pathological chemistry** or **chemical pathology.** In conjunction with anatomical pathology this field of pathology offers the possibility of a complete understanding of the origin and course of pathological processes, as well as of their nature and significance.

The extensive and many-sided domain of **Pathology** demands its practical division into various branches according to especial points of view. A knowledge of *clinical pathology* is best gained at the bedside or in the clinic, and from especial courses, lectures, and text-books. Likewise *chemical pathology* demands an especial theoretical and practical training. In this text-book **General Pathology** will be considered as including **etiology, pathogenesis,** and **pathological anatomy.** *Chemical Pathology* will be touched upon only in so far as is necessary to the understanding of the anatomical changes occurring in diseased organs.

The first part of the work, **General Anatomical Pathology,** concerns itself with the causes, origin, nature, and course of disease-processes without reference to the individual clinical forms of disease. In the second part, **Special Anatomical Pathology,** the pathological processes occurring in the individual organs and tissues are considered with especial reference to the anatomical and histological changes occurring in them.

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CHAPTER I.

The Extrinsic Causes and the Congenital Anlage of Disease.

I. The Extrinsic Causes of Disease.

1. *Origin of Disease through Deficient Supply of Food and Oxygen, through Fatigue, Heat and Cold, Changes of Atmospheric Pressure, and Electrical Influences.*

§ 1. From his birth to his death man is constantly exposed to the influences of the world surrounding him, many of these external influences being favorable to the normal exercise of his functions, while others are unfavorable.

As long as the human organism is able to offset these influences, through independent changes of its relations to the external world or through adaptation of its functions to external conditions, it will remain in health. If his regulating mechanism no longer suffices for successful opposition to unfavorable external influences, and if he cannot escape these or change his conditions of life, man becomes ill or dies.

For its preservation the body needs first of all a certain amount of food, water, and oxygen; and though it may exist for a short time without these, an **insufficient supply of oxygen, food or water** beyond a certain limit and after a certain time must of necessity lead to disease or death.

A **total deprivation or diminution of the supply of oxygen** to the tissues may take place at any period of life, either because of a lack of oxygen in the surrounding medium, or some obstruction to the entrance of the oxygen of the air into the lungs or blood, or inability on the part of the blood to take up a sufficient amount of oxygen. The fœtus *in utero* may be insufficiently supplied with oxygen as a result of diminished supply to the mother, premature separation of the placenta, disease of the placenta, or compression of the cord, whereby the interchange of gases between the maternal and fœtal blood is hindered. After birth an insufficient supply of oxygen may be due to hindrances to respiration, or the child may be so weak that its respiratory movements are insufficient to expand the lungs.

When the supply of oxygen is completely shut off, as may happen from the entrance of water or other fluid into the respiratory tract or from closure of the air-passages, the affected individual dies in a very short time from **choking** or **suffocation.** Animals confined in closed chambers die as soon as the oxygen of the air reaches two or three per cent by volume, the normal volume percentage being 20.8 (Cl. Bernard, P. Bert).

If the supply of oxygen is not wholly shut off, but only greatly diminished, as in the case of carbon-monoxide poisoning, in which the firm combination of carbon monoxide with the hæmoglobin prevents the taking up of oxygen by the red blood-cells, death by suffocation may

take place only after several days. In gradually increasing hindrances to the entrance of oxygen and resulting accumulation of carbonic acid in the blood, as in cases of narrowing of the lumen of the larynx through inflammatory exudates, compression of the trachea from goitre, weakening or obstruction of respiration, etc., a condition of breathlessness, cyanosis, convulsions, and disturbances of consciousness is produced, which is termed **asphyxia.**

If the taking up of oxygen is diminished in only a slight degree but for a long time, as in the case of a lessened number of red blood-cells in oligocythæmia, degenerative processes characterized by increased destruction of albumin and by fatty changes may occur in the tissues and organs, and these may lead not only to disease but under certain conditions to death.

Total deprivation of food and water leads to a rapid loss of body-weight, inasmuch as the fat and albumin continue to be decomposed; death finally ensues. According to Lehmann, Müller, Munk, Senator, and Zuntz, the total amount of oxidation in cases of starvation does not fall below that of the same individual in the fasting state under the same conditions. A marked decomposition of albumin and loss of water take place. In animals death occurs after the loss of about forty per cent of the body-weight, about one-half of the loss being due to the waste of muscle.

The fat disappears most rapidly; even as much as ninety-three per cent may be lost. The other organs show diminution of substance in the following order: liver, spleen, testicles, muscles, blood, intestines, skin, kidneys, and lungs. The heart, nervous system, and bones show the least loss of weight; but destruction of bone-tissue does take place during starvation, as is shown by the increase of calcium and phosphoric acid in the urine, following ingestion of water. In the blood there is a rapid diminution of the leucocytes (Luciani); the red blood-cells, on the other hand, may be relatively increased in number. The organs of animals dying from starvation show simple atrophy of the tissue-elements, particularly of the liver (Lukjanow), hyperæmia, scattered hemorrhages, degenerations, and inflammatory changes, especially in the intestine, liver, kidneys, and nervous system.

In the case of total deprivation of food and water, death occurs in man after from seven to twelve days; bodily exercise hastens the end, ingestion of water may delay it markedly, so that some individuals have been enabled through the use of water to endure a period of total abstinence from food for thirty days or longer, without dying or suffering permanent harm. The consumption of water leads to an increased excretion of nitrogen in the urine.

Life may be maintained for a long time upon insufficient nourishment, but a wasting of the body takes place which may lead to a condition of extreme emaciation, *marasmus*, or *cachexia*, and finally to death. The same thing happens when the composition of the food is unsuitable and only a portion of the necessary food-elements is present in sufficient amount, so that the body is starved either in albumin, fat, salts, or water. Dogs deprived of all nitrogenous food die in from thirty-one to thirty-four days (Magendie). When the food is abundant but poor in albumin, there occur after a time (in dogs after six weeks) loss of appetite and repugnance toward the proffered food, with impairment of digestion and assimilation (Munk). This is especially the case when the food is lacking in fat, less so when albumin or the carbohydrates are wanting.

It is very probable that the lessened absorption is chiefly due to diminished secretion of the digestive juices, this being capable of quantitative demonstration in the case of the bile. The fæces are finally nearly destitute of bile.

An insufficient supply of *iron* for a long period gives rise to anæmia and general disturbances of nutrition.

If for experimental purposes an animal well supplied with food is **totally deprived of water**, there is a rapid loss of body-weight followed in from eight to twelve days by death. The pathological changes found in the different organs are similar to those resulting from starvation. They are caused partly by lack of water and insufficient absorption of food, and partly by the retention of harmful products of metabolism.

Cow's milk has a very small iron-content. According to Fürst, milk ash contains 0.58 per cent of iron, white of egg 0.57, beef 0.7, peas 0.88, potatoes 1.18, apples 1.4, yolk of egg 1.65, lentils 2.0, plums 2.54, rye flour 2.54, spinach 3.35, lettuce 5.31, strawberries 5.89, tea 9.29, beef blood 9.79 per cent.

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§ 2. An **unusual demand** upon the **functional activity** of an organ for an **extended period of time** leads sooner or later to a state of ex-

haustion, which is, in part, due to the consumption of cell-substance, and in part to the formation of toxic products of metabolism, whereby the organ is incapacitated for further extended activity. Most often the **results of overwork** are manifested in the muscles and nervous system in the form of such symptoms as soreness and stiffness of the muscles, mental excitement, sleeplessness, heavy feeling in the head, loss of appetite, great weakness, unnatural sweating, and sometimes fever. Overwork of the heart leading to exhaustion may cause death. This may occur either when the heart is for a short time taxed to the extreme limit of its power or when for a longer period it works slightly under its maximum capacity. If the exhausted tissues are permitted to rest and supplied with an abundance of nourishment, the loss of cell-material due to the excessive activity will be replaced, the products of metabolism, which are hindering the functional activity of the tissue, will be removed, and the part restored to its normal condition.

If a tissue is frequently subjected to excessive functional demands, and if the periods of rest are too short to admit of its complete restoration, there will result ultimately a condition of permanent functional insufficiency, a chronic exhaustion, which may under certain circumstances manifest itself in a degeneration or atrophy of the affected organ. For example, a muscle through overwork may become atrophic, and a brain too constantly stimulated to activity without proper periods of rest may finally reach such a state of weakness and exhaustion that it is incapable of performing even its normal function. Through rest and properly regulated nourishment such a brain may recover; but beyond a certain limit of exhaustion the functional insufficiency may become permanent and eventually manifest itself in anatomical changes.

A very severe over-stimulation of the nervous system, even for a very short time, may under certain conditions lead to a paralysis of its functions, which, in case the heart and respiratory apparatus are affected, may cause death, but in the majority of cases is of a transitory nature.

Overwork of any organ is more quickly followed by fatigue and functional insufficiency in the case of impaired nutrition. Fatigue and insufficiency of the heart are most frequently observed when the general nutrition is lowered, as in cases of fever, or when there is deficient oxygenation of the blood, as in poorly compensated heart lesions or pulmonary diseases.

It is very probable that overwork lowers the resistance of the body to various infections.

When the functional demands upon a muscle or gland are only moderately increased, and if the nutrition is good and in proportion to the increase of labor, the **affected tissue becomes hypertrophied,** and is thereby enabled to perform the increased work permanently.

A permanent **diminution** or **cessation of activity** causes in organs that normally perform a definite and constant function (muscles and glands) a *loss of tissue-substance* (*atrophy*).

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§ 3. **High temperatures** may act, either through *local destruction of tissue* (*burning*) or through *overheating of the entire body*. The latter condition is possible only when the body is exposed to an increased temperature for such a time that it cannot protect itself from overheating by increased heat-dispersion. In dry air of from 55–60° C. (131–140° F.) the most profuse perspiration is no longer able to protect the body permanently from overheating, and in a moist atmosphere the same is true at even lower temperatures.

If the human body is subjected to high temperatures, it may become overheated, and the condition known as **heat-stroke** may result. The pulse-rate is increased, the respiration very rapid and labored, the pupils are dilated, and finally death may occur as in the case of the animals made the subject of experiment. The occurrence of heat-stroke is favored by heavy bodily labor, interference with heat-dispersion through impermeable clothing, or by a lack of water in the body.

The direct action of the rays of the sun upon the head may cause cerebral and meningeal irritation, a condition characterized by hyperæmia and inflammatory exudations, and known as **sun-stroke** or **insolation.**

The local effects of heat upon the skin, **burns,** are, according to the intensity of the heat and the time of its duration, either hyperæmia (burn of first degree), formation of a blister (second degree), tissue-eschar (third degree), or carbonization (fourth degree). The heat produces local changes in the tissues, and kills them at a certain height of temperature or after a certain time of exposure to its action.

When a large part of the surface of the body, about one-third, is burned, the affected individual usually dies, even though the burn is only of a slight degree and eschars are not formed. The anatomical findings in fatal cases of superficial burns would indicate, when death has not resulted very quickly from the severe shock to the nervous system and the overheating of the body, that the cause of death is to be sought in the changes in the blood and in disturbances of the circulation. The blood-changes consist in the loss of a portion of its water and in destruction of the red blood-cells, or in such injury to them as to diminish their function and to give rise at the same time to a deposit of the products of destruction and of hæmoglobin in the liver, spleen, and kidneys. The

changes are further characterized by a tendency on the part of the blood to stasis, hemorrhages, and intravascular coagulation, through which vessels of both the pulmonary and the systemic circulation may be obstructed, so that local tissue-degenerations and necroses may occur in certain organs, as, for example, in the kidneys, liver, mucosa of the stomach and intestine, bones, and soft parts. It is also probable that poisonous products are produced which have an injurious action, particularly upon the nervous system, liver, and kidneys.

Low temperatures act in the same manner as high ones, in part through local injury and death of tissues, in part through refrigeration of the entire body. Severe and lasting lowering of temperature causes tissue death; after mild chilling there occur, as the result of tissue-degeneration, thrombosis, hyperæmia, and exudations which are relatively rich in leucocytes. A very short refrigeration at the freezing-point is sufficient to produce degenerative changes which are quickly followed by regenerative proliferation on the part of the cells remaining uninjured. Epithelial thickenings may be produced (Fuerst) by repeated slight refrigerations (as well as by repeated slight increase of temperature). The tips of the extremities, nose, and ears are the most easily frozen. After repeated chillings of mild degree inflammatory redness and swelling of the skin, associated with severe itching, often occur (*chilblains, perniones*).

If the temperature of the entire body be markedly lowered, a condition of general paralysis results from the diminished excitability of the tissues, the nervous system and heart being especially affected. The sensorium becomes dulled, the heart-beat and respiration gradually grow weaker, and finally cease entirely. If the body be again warmed, before the excitability of the tissues is wholly lost, the power of movement in the limbs is gradually restored, and after a time consciousness returns. In man, instances of complete recovery have been observed, even after refrigeration of the body to from 24–30° C. (75–86° F.).

Besides the more severe forms of local or general lowering of the tissue temperature there may occur, as harmful pathogenic influences, mild general or local chillings, the so-called **colds**, as the result of which disease-phenomena may manifest themselves partly at the seat of chilling, partly in organs in distant parts of the body. For example, after widespread refrigeration of the skin there may occur diarrhœa, catarrh of the respiratory tract, or disease of the kidneys; after local chilling of the skin, painful affections of the deep-seated muscles. The exact relation between these phenomena and the refrigeration is unknown (the oft-repeated hypothesis that they are due to hyperæmia of the internal organs caused by the chilling of the body-surface has not been proved), but there is no reason on this account to deny the existence of diseases caused by cold. Though many diseases formerly attributed to "catching cold" have been shown to be of infectious origin, there yet remain a number of diseased conditions for which we know no other etiology than that of refrigeration. Conditions of the body in which the skin is hyperæmic and the perspiratory function active favor the taking of cold. Many individuals appear to possess a predisposition on the part of certain tissues to the effects of refrigeration; in one person certain muscles, in another the mucous membranes will be affected.

According to the view of many writers, refrigeration of the body increases the susceptibility to infection, so that, for example, the pathogenic bacteria which may be present in those cavities of the body acces-

sible from without may, after such refrigeration, be able to exert their injurious influences upon the tissue.

If rabbits are placed in well-ventilated incubators at a temperature of 36–40° C. (96.5–104° F.), their body temperature will rise to 39–40° C. (102.3–104° F.), the respiration and pulse being at the same time greatly increased in frequency. A very marked elevation of body temperature may lead in one to three days to death through paralysis of the nervous and muscular systems, the chief symptoms being a marked increase of both respiratory and cardiac activity. If the increase of body temperature is not greater than 2–3° C. (3–5° F.), the animals may, if properly nourished, live from ten to thirty days or even longer, but they will lose in weight and ultimately die, showing before death a gradually increasing diminution of hæmoglobin and of red blood-cells. Degenerative changes, particularly fatty degeneration, occur in the liver, kidneys, and heart muscle. During the experiment there is an increased production of urea.

The fact that man dies so frequently after an extensive superficial burn of the skin has been explained in various ways. *Billroth*, *Foà*, *Mendel*, and others believed the cause of death to lie in a suppression of the perspiration and the resulting accumulation of toxic substances in the blood; while others, as *B. Sonnenburg* and *Falk*, sought the cause in a reflex lowering of the vascular tone. In the foudroyant cases, according to *Sonnenburg*, the overheating of the blood causes a paralysis of the heart. *Ponfick*, *Klebs*, *von Lesser*, and others, on the other hand, are of the opinion that the fatal issue is due to injury and destruction of the red blood-cells. *Silbermann*, *Welti*, and *Salvioli* also seek the cause of death in an injury to the blood, emphasizing, however, not so much the destruction of the red blood-cells as the occurrence of stasis and coagulation of the blood in the vessels of different organs, which are interpreted as resulting from the changes in the blood. On the other hand, *Kijanitzin*, *Parascandolo*, *Scagliosi*, and *Dorn* hold that there is formed in the bodies of burned individuals a poison which has an injurious action upon the nervous system and also upon the liver and kidneys. *Wilms* seeks the cause of death partly in a loss of the water of the body and partly in the absorption of poisonous products from the burned area.

According to *Pflüger* and others, all the vital processes may be brought to a standstill through refrigeration, without its being impossible for a recovery to take place from the apparent death. This may happen even when the animal is frozen to a solid mass. *Preyer* also holds the opinion that the continuity of life may be wholly interrupted by refrigeration, and designates subjects who are thus "lifeless," but still capable of living, as *anabiotic*. Frogs are said to remain capable of life for many hours, even though the temperature be reduced to −2.5° C., at which temperature the heart is frozen. According to the investigations of *Koch*, such anabiosis of solidly frozen animals is possible when only a portion of the water contained in the body of the animal is frozen and when the thawing process takes place slowly. In the case of rapid thawing, strong diffusion currents are set up between the water coming from the ice-crystals and the concentrated albuminous solutions of the blood and the tissues; and these currents may exert a damaging effect upon the latter.

According to the investigations of *J. Dewar* (*Proc. of the Royal Soc.*, London, 1900), the seeds of wheat, barley, mustard, peas, and pumpkins do not lose their germinative power when put into liquid hydrogen; that is, in a temperature of −250°. Further, the protoplasm under these conditions was not changed by the cold.

Not only do the heat-rays of the sun-light or the arc-light affect the human body, but their **chemically active violet and ultraviolet rays** have also an important action upon its tissues. According to *Young*, *Beclard*, *Schnetzler*, *Godnew*, and others (for literature see *Sack*, *l.c.*), the processes of growth and regeneration are carried on more rapidly under the influence of blue and violet rays than under ordinary conditions. According to *Finsen*, variola-lesions in the skin run a much more favorable course when protected from the violet rays by means of red glass. According to the investigations of *Maklakow* the violet and ultraviolet rays of the arc-light can produce a peculiar erythema of the skin, even when the heat-rays are excluded (*Widmark*). *Finsen* holds that "sunburn" is produced chiefly by the violet and ultraviolet rays. Bacteria in plate-cultures are killed within a short time by exposure to the ultraviolet rays of the arc-light. According to the investigations of *Godnew*, *Finsen*, *Möller*, and others, the violet and ultraviolet rays penetrate the skin, but are absorbed by the blood. Basing his views upon these facts, *Finsen* has attempted to treat skin diseases, especially lupus, cancer, vascular nævi, acne, etc., with the ultraviolet rays of the sun and the arc-light, and has been very successful with the latter method. Fresh cases of lupus were healed by it in a relatively short time. The heat-rays are excluded by means of the interposition of quartz lenses and chambers of running water. A hollow lens of quartz through which water is flowing is pressed firmly against the affected area in order to exclude the blood which absorbs the ultraviolet rays. The irradiation, when

continued for about an hour, causes first an inflammation, leading after twelve hours or more to the formation of a blister. Later, scar tissue develops in the area so treated.

According to investigations by *Dreyer*, and confirmed by *Neisser* and *Halberstaedter*, infusoria, bacteria, and animal tissues when impregnated with erythrosin (solution of 1: 1,000–1: 4,000) become sensitized to red and yellow rays, so that these rays act upon them in the same manner as the violet and ultraviolet. Since the red and yellow rays possess a greater power of penetration into the tissues, a more marked and deeper effect of irradiation can be obtained by the previous treatment of the tissues with solutions of erythrosin.

Roentgen-Rays, acting upon the skin for some time, cause in the exposed portions, at point of entrance and exit, degenerative changes affecting chiefly the epithelium, but also the connective-tissue cells. These are followed by inflammatory processes. Clinically these changes show themselves usually about fourteen days after the exposure, and reach their acme after some weeks. The hair and finger-nails may be lost. If tissue-necrosis occurs, the healing of the resulting ulcer is very slow and difficult. The Roentgen-rays have also been used with some success in the treatment of lupus and carcinoma of the skin. Exposures of 30 to 60 minutes are given, and repeated two or three times. After one or two weeks the cancer shows an inflammatory reaction. Healing of the neoplasm takes place through the destruction of the carcinoma cells, which are especially susceptible to the action of the rays; and the resulting ulcer heals through the formation of scar-tissue and a regeneration of the epidermis. In the case of carcinoma of the mamma a certain amount of destruction of the neoplasm may be accomplished, but not to the extent of a complete cure. Recent cases have been observed of cancer developing in skin frequently exposed to Roentgen-rays.

According to investigations by *Heineke* and *Warthin*, the experimental irradiation of rats, mice, guinea-pigs, rabbits, and dogs causes, even after fifteen-minute exposures, a marked destruction of the lymphoid cells of the spleen, bone-marrow, and lymph-nodes. The disintegration of the lymphoid cells is evident almost immediately after the exposure, and persists for some hours. After single exposures regeneration is rapid, but after prolonged or repeated exposures the spleen may finally become practically devoid of lymphoid cells. In exposures of this degree the death of the animal usually takes place within ten days, after it has exhibited marked symptoms of intoxication. Small animals may be rendered blind by prolonged exposures. In the use of Roentgen-rays as a curative agent in leukæmia it has been shown that the size of the spleen may be greatly diminished, the white-cell count brought down to normal, the general condition improved, and the life of the patient extended by one to two years. *Warthin* has shown that this improvement is due wholly to the destructive action of the rays upon the white cells of the blood-cell-forming organs, and that the essential disease-process is not cured. He has also emphasized the dangers of an intoxication arising from the products of proteid disintegration, and has shown the occurrence of extensive degeneration and calcification of the kidneys in cases so treated. His investigations show also that slight changes occur in the renal epithelium as the result of short exposures. *Capps* believes that a leukotoxin is produced in the sera of animals exposed to the rays. *Scholz, Seldin, Philipp, Halberstaedter,* and others have demonstrated the production of azoöspermia in man and animals by means of Roentgen irradiation. Numerous cases of sterility in Roentgen-ray operators have been observed. *Bardeen* found that the death of spermatozoa is hastened by irradiation, and that spermatozoa injured by short exposures to Roentgen-rays, but still capable of fertilization, may cause the development of monsters from ova fertilized by them. He concludes that nuclear material may be so influenced by exposures to the rays that after a latent period it may show marked abnormalities in development. *Foersterling* warns against the dangers of irradiation in young children. *Edsall* has reported an instance of death following Roentgen irradiation, and the present tendency is to regard the rays as agents capable of producing serious damage to the animal organism.

Becquerel-Rays act similarly to the Roentgen. Tissue-degenerations and inflammations appear in the second or third week after the exposure and reach their acme in 20–30 days (*Halkin, l.c.*). Slowly healing ulcers may be formed. Some success has been obtained with the rays in the treatment of cancer of the skin and lupus. According to *Pfeiffer, Friedberger*, and *Scholtz* the rays are bactericidal, and a portion of the active rays can penetrate the tissues to a depth of several millimetres. Roentgen and Becquerel rays are not, like light, heat, and electricity, especial forms of undulations of the ether, but consist of extremely minute particles of matter, electrons, which are given off into space with great rapidity. In the case of the Roentgen-rays the projecting power is the electrical energy supplied to the Roentgen tube. The Becquerel rays represent a property of certain bodies designated by Becquerel as *radio-activity*. In 1896 this investigator discovered that uranium and its salts give off rays that act upon photographic plates in the dark and are capable of penetrating bodies impervious to

light. In 1898 *Madame Curie* succeeded in separating from pitchblende two radio-active bodies which were named *radium* and *polonium*. In 1899 a third radio-active body (*actinium*) was discovered by *Curie* and *Debierne*. Radium has been produced in a pure form and has been the most carefully studied. It is a new element, the salts of which are radio-active in the highest degree and project electrons into space at a velocity of 160,000 kilometres per second, at the same time giving off heat-rays. The air about it becomes ionized, that is, becomes a conductor for electrical discharges. The action of radium upon the tissues is similar to that of Roentgen-rays.

According to *Hinstedt* (*Ann. der Physik*, 1903), numerous springs, hot ones in particular, are radio-active, and it is not improbable that their special action is in part dependent upon this property.

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§ 4. A sudden **lowering of atmospheric pressure,** as in the case of mountain-climbing and balloon ascents, may cause conditions of great exhaustion, with marked palpitation of the heart, unconsciousness, irregular breathing, and sometimes vomiting, and bleeding from the gums and lips. These symptoms depend essentially upon a *lack of oxygen* (P. Bert), the capillaries of the lungs being unable to take up sufficient oxygen from the highly rarefied air. Kronecker believes that they are to be referred to disturbances of the pulmonary circulation. According to the investigations of Schumburg and Zuntz, it appears that a given amount of labor calls for a greater amount of oxygen at an increased elevation than at a lower level. The symptoms of mountain-sickness appear at a lower elevation than those of balloon-sickness, owing to the demands made upon the muscles in the former case during the climbing. During the building of the Gorner Grat Railway it was found that at a height of 2,700–3,000 metres the capacity of the laborers was diminished to a third.

According to the researches of Egger, Miescher, and others, a sojourn in high altitudes leads, after a short time, to an increase in the number of red cells and a greater hæmoglobin-content of the blood.

Schaumann and Rosenquist hold that the same phenomenon may be observed in animals confined for some time in bell-jars at a lower atmospheric pressure. Other authors (Schumburg, Zuntz, Gottstein) oppose this view, and maintain that the phenomenon is due either to a thickening of the blood from loss of water and to changes in the distribution of the blood, or to changes in volume of the measuring-apparatus; they endeavor to explain the favorable effects which many individuals expe-

rience from a residence at high altitudes by certain stimulating influences (greater exposure to sun's rays) which affect the nervous system and cause increased metabolism. According to Marti, *intense and prolonged irradiation* of the body stimulates the formation of red blood-cells and to a lesser degree also that of the hæmoglobin.

A sojourn in diving-bells or caissons, such as are employed in building operations beneath the water, in which the **atmospheric pressure is increased,** under certain conditions, as high as four atmospheres or even greater, causes a slight difficulty in breathing and a relatively unimportant increase of the pulse-rate. If a change be made quickly from the compressed atmosphere to air of ordinary pressure, there may occur within an hour a condition of great fatigue, tightness of the chest, ringing of the ears, cramps in the muscles, pains in the joints and limbs, hæmorrhages from the nose, ears, and lungs, dilatation of the pupils, and under certain conditions paralysis, coma, delirium, and even death after an interval of from one to twenty days. The cause of these phenomena is probably to be found in the obstruction of blood-vessels of the spinal cord by bubbles of nitrogen that has been absorbed under the high pressure (Hoche). According to experimental investigations of Heller, Mager, and von Schrötter, the blood, after rapid removal of pressure, contains free gas (almost exclusively nitrogen), so that free gas circulates in the blood. In fatal cases associated with paralysis areas of degeneration (Nikiforoff) are found in the white columns of the spinal cord, in which individual nerve-fibres present marked changes in the form of swelling of the axis cylinders, and disintegration of the medullary sheaths, with the formation of vacuoles in the place of the nerve-fibres that have been completely destroyed. If the gray matter is involved, the ganglion-cells may also degenerate.

Fig. 1.—Lightning-figures on the shoulder, breast and arm of a woman struck by lightning.

Changes in the electrical condition of the atmosphere and in the magnetic state of the earth have no demonstrable influence upon the human body; on the other hand, **electric discharges,** as lightning-stroke, may cause, in part, local lesions of the skin resembling burns (Fig. 1), hæmorrhages in the skin, and burning of the hair, and, in part, lesions of the whole body. Under certain circumstances lightning-stroke causes laceration of internal organs, as, for example, of the heart and liver. The most frequent and important effect of lightning-stroke is a **paralysis of the nervous system,** which gives rise to a severe dyspnœa, which may be fatal immediately or after a few minutes or hours, or may gradually pass away after several hours, days, or weeks. Only rarely do individual nerve-trunks remain permanently paralyzed. A transitory paralysis may occur when the electrical discharge has not passed through the body, but has descended in its neighborhood.

In individuals who have been struck by lightning there may be found

slight or severe burns of the skin corresponding to the points of entrance and exit of the current, and various injuries to the tissues in the course of its path through the body. The marks of the burn are for the greater part red, and form peculiar branching zigzag lines, the so-called *lightning figures* (Fig. 1), which are essentially a hyperæmia, and soon disappear if the burns are not severe.

The passage of **powerful electric currents of high tension,** such as are generated by dynamos, through the human body, as may happen when an individual is placed in a circuit or comes into contact with an uninsulated conductor, may give rise to severe disturbances or cause death. According to Kratter, the lower limit of danger occurs at a tension of about five hundred volts. Alternating currents are much more dangerous than continuous ones of the same strength and tension. When the effects are not fatal, the injured person is suddenly rendered unconscious, this condition lasting for a few minutes or several hours, and for several days afterward symptoms of vertigo, prostration, headache, and palpitation of the heart may persist (Kratter). At the points of contact more or less severe burns are produced.

In fatal cases, death takes place suddenly or rarely after ten or thirty minutes. The autopsy findings, aside from the burns at the points of contact, are evidences of suffocation and hypervenosity of the blood, stasis of the blood within the thoracic vessels, and often small scattered hæmorrhages which are due partly to the direct action of the current. The cause of death is paralysis of the centre governing the respiration or the heart's action.

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2. *The Origin of Disease through Mechanical Influences.*

§ 5. **Traumatic influences of various kinds** leading to **concussion, bruising, and laceration of tissue** are of very frequent occurrence, and act partly through the tearing and destruction of tissue, partly through changes in tissue-organization not recognizable to the naked eye, and partly through lesions and ruptures of the blood- and lymph-vessels, and through irritation and paralysis of nerves. The sequelæ are partly *necrosis* and *destruction* of tissue, partly *disturbances* of *circulation, inflammation,* and *regenerative proliferations.* Frequently repeated *mechanical traumatisms of slight degree, such as rubbing,* may give rise to *congestive hyperæmia* and *inflammations,* which may lead further to *hyperplastic growths of tissue.* If large quantities of insoluble *dust particles* are continuously taken into the lungs indurations of the pulmonary tissue may develop in consequence. As a result of prolonged *pressure* and *diminution of space,* atrophy of an organ or tissue may occur (corset-liver).

After a single or after frequently repeated trauma, there may develop under certain conditions at present unknown to us, malignant new-formations of tissue called *tumors.* Trauma may further pave the way for an *infection,* either in that the wound caused by the trauma is *infected at the time of injury* or *is secondarily infected from without;* or that *micro-organisms were previously present* in the body under conditions inhibiting their growth, and these find in *the injured tissues a suitable soil for growth,* so that to the trauma an infection is joined.

Traumatic influences affect, first of all, the **external parts of the body;** but it may happen, either with or without visible injury to external parts, that **internal organs** may be injured, and the internal lacerations, necroses, and hæmorrhages thus produced, may be followed, not only by inflammations and reparative tissue proliferations, but also by malignant neoplasms, and by infective processes.

Mechanical lesions (also thermal, electrical, and corrosive) run a special course, if through the local injury the **nervous system** becomes involved. Such involvement occurs either through the direct action of the trauma upon the central nervous system; or, by the stimulation of the sensory or sympathetic nerves, the central nervous system may be so affected that a number of additional nervous symptoms follow.

If the direct concussion of the cranium is followed by paralysis of the cerebral function and unconsciousness, the condition is termed **commotio cerebri** or **cerebral concussion.** This term is especially used

when the trauma has produced no visible changes in the structure of the brain, or at least none of any size or importance.

Excessive stimulation of the peripheral nerves may cause a reflex inhibition or paralysis, involving chiefly the functions of the heart and respiratory apparatus; the symptoms thus produced being collectively designated as **shock.** The most frequent causes of shock are injuries to the spinal column, abdominal cavity, and scrotum, less frequently to the extremities and thorax. Further, shock may be caused by lightning-stroke, burns, corrosions of the skin, fear, and psychical emotions through whatever avenue of perception they may be called forth. Individuals whose nervous systems are in a certain condition of excitement are especially liable to shock; conditions of narcosis and drunkenness inhibit its occurrence.

Shock is characterized chiefly by weakened energy on the part of the heart and irregular breathing, which lead to a decrease in the interchange of gases in the tissues and to a lowering of the temperature (Roger). The consciousness is usually preserved, the skin and visible mucous membranes are pale, the pulse is small and markedly quickened, often irregular and intermittent.

Further, the individual suffering from shock may be either excited, groan, shriek, and complain of a fearful anxiety associated with dyspnœa (*erethistic shock*); or he may lie quiet, with sunken countenance, and exhibit evidences of great weakness of both sensory and motor functions (*torpid shock*). In severe cases death takes place from the stoppage of the heart and cessation of respiration.

Shock, in being due to the over-stimulation of the peripheral nerves, is closely allied etiologically to the phenomenon known as **syncope**; but the last-named condition differs essentially from shock in that its chief symptom is a transitory loss of consciousness, while the functions of the heart and respiration show no marked disturbance. Syncope is, further, usually preceded by prodromal symptoms, such as dizziness, ringing in the ear, and darkening of the visual field, these being absent in shock.

Not infrequently, following an injury to some part of the body, there may arise a more or less pronounced functional disturbance of the nervous system, which may often persist long after the local injury has healed, so that such disturbance is in no way dependent upon anatomical changes in the peripheral or central nervous system, but must be regarded as a *purely functional disturbance* of *psychical origin.* Such conditions are termed **traumatic neuroses** or **accident nervous diseases,** and are characterized chiefly by subjective but in part also by objective symptoms. To the first belong especially pains not definitely localized at the seat of injury, as headache, pain in the chest, backache, difficulty in movement, general lassitude, inability to perform mental labor, dulness of perception, disturbances of sight, flashes before the eyes, dizziness, restless sleep, loss of appetite, and disturbances of digestion. With these last symptoms are associated psychical depression of a hypochondriacal or melancholic character, irregularly placed areas of cutaneous anæsthesia, enfeeblement of the senses of taste, hearing, and smell, motor paralysis, cramps, and hyperæsthesia, concentric narrowing of the visual field, pareses, muscular spasms, tremors, acceleration of the pulse, and tendency to sweating.

All of these phenomena depend essentially upon a psychical shattering of the perceptive life, a **psychoneurosis** which is less often due to the trauma and the associated psychical shock than to the resulting anxi-

ety over health and business matters. The condition in part partakes of the nature of *hysteria,* as characterized by a disturbance of the normal relation between the mental and bodily processes; in part of *hypochondria,* as recognized by the spontaneous occurrence of abnormal sensations; and in part of a *neurasthenia,* which reveals itself by the production of abnormal pathological sensations through relatively slight stimulation or exertion. If the will no longer controls the motor centres, hysterical paralyses arise; if the normal control and inhibition of the will are lost, so that unreasonable will-stimuli are created and influence the muscles, hysterical twitchings, contractures, or convulsions take place. If a nervous stimulus arising in the sensory tract fails to reach the consciousness, there follows a hysterical anæsthesia; if there arise in the consciousness the images of expected or feared sensations, and if these images are intensified into actual subjective stimuli of consciousness, hysterical pains and neuralgias result (Strümpell).

Rosenbach designates as **kinetoses** those diseases which arise when energetic and continuous movements of the body in one direction are changed into the opposite direction, so that a shifting of the internal organs results. In this class belong the pathological phenomena observed in *seasickness*, and in the conditions caused by *see-sawing, whirling, movement in a vertical direction,* and *sudden stoppage of motion.* As a result of the rapid change in direction of bodily motion, the molecules which are moving in the line of the primary direction are forced to move in the opposite direction; and, according to Rosenbach, such a change is sufficient to cause more or less important molecular disturbance. He explains the symptoms of seasickness, as, for example, the abnormal secretion of the stomach, the increase of intestinal peristalsis, the vomiting, etc., as the results of purely mechanical influences on the tissues, and believes that the liver, intestine, brain, and nerve-plexuses are similarly affected through mechanical influences acting upon their protoplasm. On the other hand, *Binz* refers seasickness to an acute anæmia of the brain which causes the nausea and vomiting. A horizontal position and the administration of a water solution of chloral hydrate, which dilates the arteries of the head, have a favorable action upon the condition.

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3. *The Origin of Disease through Intoxication.*

§ 6. By **poisoning** or **intoxication** is meant that *impairment of health, caused by the injury to a tissue, which certain substances, by virtue of their chemical nature, are able to produce under certain conditions.* Such sub-

stances are termed **poisons**, and are derived partly from the mineral kingdom, partly from the vegetable, and partly from the animal kingdom. They may occur in a natural state or they may be produced artificially from inorganic or organic substances. Many of the most important poisons are products of either plant or animal life, and are formed either within the tissues of the plant or animal, or from their food-supply by the transformation of substances which are either inert or possess an entirely different action.

The *most important poisons belonging to the mineral kingdom or which are produced from minerals are:* metallic mercury, chlorine, bromine, iodine, sulphur, and various combinations of these substances, different combinations of arsenic, antimony, lead, barium, iron, copper, silver, zinc, potassium, sodium, chromium, etc. Of the *poisons containing carbon, which are artificially produced*, the most important are: chloroform, chloral hydrate, ether, alcohol, iodoform, carbon bisulphide, hydrocyanic acid, potassium cyanide, oxalic acid, nitroglycerin, amyl nitrite, petroleum, carbolic acid, nitrobenzole, picric acid, and aniline. It may be observed in this connection that modern chemistry is constantly producing new substances, some of which are poisons.

Of the *poisons produced by plants of the higher order*, those of chief importance are: the *vegetable alkaloids*, such as morphine, quinine, colchicine, atropine, hyoscyamine, veratrine, strychnine, curarine, solanine, nicotine, digitaline, santonin, aconitine, cocaine, coniine, muscarine, and ergotine, all of which in relatively small doses may cause poisoning.

The *lower forms of plant life, especially bacteria, produce an extraordinary variety of both poisonous and non-poisonous substances, out of the food material in which they develop.* Some of these substances are similar to the vegetable alkaloids, others to the ferments, and are therefore designated *toxic cadaveric alkaloids, toxic ptomaïns, toxins*, and *toxenzymes* (compare § 11). It may happen that the blood, flesh, or any organ of a healthy animal may acquire poisonous properties through the presence in it of poisonous products of bacterial growth. Such diseases due to bacterial poisons in the food are known as *botulismus, sausage, meat, fish,* and *cheese poisoning.* These conditions are to be explained, in part, by the growth of bacteria (*B. botulinus*) in the food-stuff and the formation of poisonous products, true toxins (§ 11); in part by the fact that germs were present in the tissues of the animal before death, the animal being slaughtered while diseased, and the use of its flesh as food causes either poisoning or the same disease as that affecting the animal. Under certain conditions foods which are not spoiled may already contain bacteria, and these may develop in the intestine of the individual eating the food and cause poisoning through the production of toxins, or enzymes.

According to Lombroso, the disease *pellagra*, which is of common occurrence in Italy, Roumania, and Greece, is caused by the eating of decomposed corn. The disease *kakké* or *beri-beri*, which is endemic in Japan, is regarded by Miura and Yamagiva as due to the extended use of rice which has been spoiled in drying.

Among the *animals which normally produce poisons within certain tissues of their bodies*, the best known are: serpents, toads, salamanders, fish, mussels, oysters, scorpions, Spanish flies, and many stinging insects.

Certain forms of sea-fish are poisonous at all times, others only at certain periods, and observations have been made particularly of such fish found in Japanese waters. According to *Saotschenko*, the poison of many poisonous fishes is secreted by certain

skin-glands found at the roots of the dorsal and caudal fins, and may be found also in the eggs of such fish. According to *Remy*, *Miura*, and *Takesaki*, the poison is secreted in the sexual glands alone in the case of the poisonous fish belonging to the family Gymnodontes (tetrodons). According to *Mosso*, there is found in the blood-serum of eels a toxic substance (ichthytoxin) which, when introduced into the small intestine of animals experimentally, causes symptoms of poisoning and may kill the animal. According to *M. Wolff*, the liver of mussels (*Mytilus edulis*) contains the poison; its action, according to *Schmidtmann*, *Virchow*, *Salkowski*, and *Brieger*, is similar to that of curare. *Brieger* has also shown that from the poisonous mussels there can be obtained basic substances closely related to ptomains, the basic products of decomposition. To what extent the causes of the production of poisons in poisonous fishes and mollusks are to be ascribed to normal and to what extent to pathological processes of life cannot at the present time be always decided. From the fact that the mussels and oysters are poisonous only in certain places where the water is impure, and as the starfish found in the same localities are similarly affected, it is probable that the poisonous action of these mollusks may in part be due to their contamination with bacteria or to the occurrence of certain diseased conditions.

The *venom of serpents* is formed exclusively in the poison-glands lying in the upper portion of the corner of the mouth. It is a green or yellowish fluid and its activity is not influenced by drying or by preservation in spirits.

Snake venom, the poison of spiders and toads and of the blood of the eel and muræna, ricin (obtained from the seed of the castor-oil bean), and *abrin (from the seed Abrus precatorius)* show properties similar to those of the bacterial toxins (compare §11). Snake-poison and that of the blood of the eel have also a hæmolytic action.

It is difficult to give an exact definition of poison and poisoning, since the action of the substances considered in this connection varies greatly according to the dose and attenuation, as well as the method of introduction into the tissues of the body. The most powerful poisons when introduced in minute doses may not only be harmless, but may exert a beneficial or curative effect. On the other hand, substances which are not usually classed with the poisons, such as the non-corrosive sodium salts, when introduced into the body in large quantities or in concentrated solutions, may produce effects which must be regarded as of the nature of poisoning. Further, poisons in certain dilutions (phenol) may serve as food-material.

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See § 12 for literature of Ptomaïns and Toxins.

§ 7. **Poisons** may be divided according to their action into three groups: first, those producing local tissue-changes; second, those acting injuriously upon the blood; third, those affecting chiefly the nervous system and the heart without producing recognizable anatomical lesions.

The **poisons which cause marked local lesions** injure primarily the tissues with which they first come into contact upon entering the body. If such poisons are diffused by means of the body-fluids, the most diverse organs and tissues may be injured; but their action is usually limited to that organ in which they are stored up or through which they are excreted, especially the liver, intestine, and kidneys.

The primary seat of injury is most often the mucosa of the upper portion of the intestinal tract and the respiratory passages, but in many cases the skin is first affected. Very frequently poisons, which are employed for disinfecting, are brought into contact with wounds for the purpose of killing bacteria or preventing their growth, and in this way may cause local changes or may be absorbed and damage the internal organs or the entire body.

The first great group of poisons belonging to this class are those which cause marked tissue-changes at the primary point of contact, which are similar to those of burns, and for this reason have been designated **caustics or corrosives.** If the action of a caustic reaches its most characteristic severity, the affected tissue will be wholly destroyed and converted into either a dry, hard eschar, or under certain conditions into a moist, soft slough. If the action is of moderate intensity as the result of a less concentrated solution of the caustic agent, or of incomplete action of the chemical even when applied in strong solution or in substance, or because the tissue itself is more resistant as in the case of the skin, the changes produced are much less severe, and are characterized by redness, swelling, inflammation, and hæmorrhages. Very diverse changes are often found in the same organ, such as local sloughing (necroses), hæmorrhages, inflammations, and small swellings due to local hyperæmia. If the changes have existed for some time, the local eschars are surrounded by a more or less marked inflammatory zone, which in the case of certain caustics may be of very limited exent.

The substances belonging to the class of caustic poisons are: first, the *corrosive acids*, sulphuric, nitric, hydrochloric, phosphoric, oxalic, arsenic, arsenious, osmic, acetic, lactic, trichloracetic, carbolic, and salicylic acids; and further, the *corrosive combinations of the alkalies and alkaline earths*, potassium and sodium hydroxide (watery solutions of KOH and NaOH), caustic ammonia (solution of NH_3 in water), ammonium carbonate, caustic lime, and barium sulphate. Belonging in this class are also certain *corrosive salts*, chiefly of the heavy metals, such as salts of antimony (tartar emetic and antimony trichloride), salts of mercury (corrosive sublimate and red precipitate), nitrate of silver, zinc chloride, zinc sulphate, copper sulphate and copper acetate, aluminum acetate, potassium chromate and bichromate, and chloride of iron.

The *poisons belonging to this class derived from animals* are: cantharidin, from the beetle *Lytta vesicatoria;* phrynin, the secretion from the cutaneous glands (parotid) of the toad; the secretions from the poison-glands of snakes and scorpions; the secretion of the sting-gland of bees, wasps, and hornets; the secretion of the salivary glands of stinging-gnats, flies, and gad-flies; and the secretion of the poison-glands of the maxillary palpæ of spiders (tarantula)—all of which cause local necrosis, or hæmorrhage and inflammation. Many of the *higher plants* produce in their blossoms, seeds, stems, or roots substances which, when brought into contact with the tissues, cause local irritation and inflammation, as, for example, daphne, different forms of *Ranunculus*, varieties of anemone, *Primula obconica* (pubescent portion), marsh-marigold, different varieties of *Calla*, dragon-root, *Croton tiglii* (from the seeds of which croton-oil is obtained), buckthorn (*Rhamnus cathartica*), black elder (*Rhamnus frangula*).

The nature of the local changes which these substances and many others not

mentioned here produce is naturally very varied, and is dependent partly upon the activity of the poison, and partly upon the location and manner of application. The mineral acids, solutions of caustic potash and mercuric chloride, when concentrated, cause marked tissue-eschars, associated with hæmorrhagic inflammations, especially when taken into the stomach. Through the action of acids there is a marked withdrawal of the alkaline constituents of the body fluids, leading to disturbances of respiration and circulation. The venom of snakes causes usually severe local inflammations and hæmorrhages, which often extend far beyond the region of the bite, and sometimes may cause also a widespread gangrene. There are also snake-venoms which produce only insignificant local changes, the general symptoms of poisoning being much more prominent. The *volatile* or *gaseous* poisons, which in the form of gas or vapor cause local irritation of the tissues, affect chiefly the mucous membranes of the eye and respiratory tract (*irrespirable gases*). To this class belong especially the fumes of ammonia, chlorine, sulphurous acid, nitric oxide, nitric dioxide, nitric trioxide, osmic acid, formalin, and mustard-oil. The intensity of action of these poisons is very varied, often causing only a transitory hyperæmia, but being able also to give rise to tissue necrosis and severe inflammation. The irritation of the respiratory tract gives rise to coughing and a spasmodic narrowing of the glottis which may interfere with breathing.

To the local irritation and inflammation caused by these poisons at the primary seat of contact may be added further *effects upon internal organs*. After the absorption of these poisons into the fluids of the body, those organs suffer most in which the poison is stored up or elaborated, though organs of the most varied structure may be affected, as well as those not concerned in the excretion of the poison. In the case of certain poisons, the changes at the point of entrance are very slight and often not recognizable, the important anatomical lesions occurring first in other tissues, to which the poison has been carried by the blood. Finally, a given poison may act also as a *nerve and heart poison*, so that clinically the effects of this action are much more prominent than the local lesion. In poisoning with *corrosive sublimate*, cell necrosis takes place in the secreting part of the kidneys, and there is also severe inflammation of the colon. The salts of *chromic acid*, *cantharidin*, and many *acids* cause more or less marked degeneration and inflammation in the secreting portion of the kidney and in the urinary passages.

Phosphorus, *arsenic*, *antimony*, and *pulegon*, which have but slight corrosive action, produce tissue-degenerations, particularly fatty degeneration, and also hæmorrhages, in the kidneys, liver, heart, muscles, bone-marrow, and capillaries of different organs, these changes being particularly marked in cases of phosphorus poisoning. According to *Meyer*, the cause of the tissue-degenerations in phosphorus poisoning is to be sought in its action upon the cardiac nervous system and the consequent disturbances of circulation. *Tischner* believes that there is a lesion of the peripheral nervous system.

If an individual is exposed for months or years to the fumes of yellow phosphorus, there may take place an inflammation of the jaw bones leading to necrosis, but only when the occurrence of inflammatory changes is favored by other causes, such as putrid decomposition in the mouth or the presence of decaying teeth.

The long-continued use of *silver nitrate* may be followed by a deposit of black granules of silver in the most diverse tissues, the skin, kidneys, intestinal villi, and the choroid plexus.

The *venom of snakes* possesses, in addition to its local effects, a paralyzing action upon the nervous system and heart, and may cause death through paralysis of the respiratory centre.

Soluble salts of *lead* when ingested may cause irritation and inflammation of the intestine, with such symptoms as vomiting, diarrhœa, constipation, cramps in the stomach, associated with such nervous phenomena as anæsthesia, motor paralysis, convulsions, vertigo, and loss of consciousness. When ingested continuously for a long time, lead gives rise to anæmia (*Jores*), general disturbances of nutrition, intestinal colic, pains in the limbs, anæsthesia, motor paralysis, cerebral disturbances, and kidney disease. These disturbances are without doubt dependent upon the distribution and deposit of lead throughout the body, leading to anatomical lesions of varied nature.

The active principles of *ergot* (*Secale cornutum*), *sphacelinic acid* and *cornutin*, when taken in large doses, or when repeatedly eaten in bread, cause itching, pain, and cramps in the limbs, followed by numbness and feeling of cold in the toes and finger tips, and finally there may also occur a more or less extensive gangrene of these parts (*ergotism*, "*Kribbelkrankheit*"); at the same time ulceration of the intestine may occur. In cases of chronic poisoning, degenerations of the spinal cord take place (*Tuczek*). The feeding of chickens with ergot causes gangrene of the comb through

the production of stasis and hyaline thrombosis in the blood-vessels. In animals fed for a long time with ergot degenerative changes are found in the central and peripheral nervous system, in the blood-corpuscles, and in the endothelium of the blood-vessels (*Grigorjeff*).

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§ 8. The *poisons which affect the blood chiefly*, and are therefore termed **blood-poisons**, are partly gases and partly fixed substances. The latter are absorbed chiefly from the intestine, but they may also enter the body through wounds, or they may be injected directly into the blood-vessels. Some of the blood-poisons may also produce local lesions in the tissue at point of entrance; further, there may be joined to the action on the blood a direct effect upon the nervous system, which under certain conditions may cause death before the action upon the blood is recognizable. Finally, it should be emphasized that the blood-changes produced by the poison may cause numerous secondary changes in different organs, for instance, in the kidneys, liver, intestine, and brain.

Carbon monoxide, hydrocyanic acid, potassium cyanide, and hydrogen sulphide form combinations with hæmoglobin giving rise to carbon-monoxide-hæmoglobin, cyan-methæmoglobin, and sulphur-methæmoglobin, thereby inhibiting or destroying the functional capacity of the red blood-cells. They also produce an effect upon the nervous system which is most marked in the case of hydrocyanic acid and potassium cyanide. These poisons in very small doses paralyze the central nervous system, producing death almost immediately through paralysis of the centres of respiration and circulation.

Potassium chlorate, toluylendiamin, hydrazin, nitrobenzol, nitroglycerin, amyl nitrite, picric acid, phallin (a poison obtained from the mushroom, *Agaricus phalloides*), *helvellic acid* (poison of *Helvella esculenta*), *extractum filicis maris æthereum, arseniuretted hydrogen*, and other substances cause destruction and hæmolysis of the red blood-cells and lead in part to the formation of methæmoglobin, that is, to an oxygen combination of hæmoglobin, the oxygen content of which is the same as that of oxyhæmoglobin, but in which the oxygen is bound more firmly than in the latter.

Certain *bacterial products* which are called *bacterial hæmolysins* have also a specific action upon the red blood-cells, leading to the production of hæmoglobinæmia. The best known are those occurring in infections with the tetanus bacillus and staphylococcus and are known as tetanolysin and staphylolysin.

When the blood of an animal is introduced into the blood stream of man or of an animal of another species, *specific hæmolysins* become active, that is, poisons which cause hæmolysis of the foreign red blood-cells.

Carbon-monoxide poisoning most often results from the carbon monoxide in coal- or illuminating-gas, but may occur under other conditions, as in the case of vapors produced by gun-powder or gun-cotton. The effects of the inhalation of carbon monoxide result from the combination of the gas with the hæmoglobin of the blood and the formation of carbon-monoxide-hæmoglobin. The amount of oxygen combined with the hæmoglobin is thereby decreased, and the taking up of oxygen is reduced, even when the respired air contains only 0.05 per cent or even 0.02 per cent of CO (*Gruber*). The red blood-cells themselves present no changes. A rapid supply of carbon monoxide to the nervous system may cause direct injury to the nerves, giving rise to convulsions and later to paralysis (*Geppert*). In cases of long-continued poisoning the displacement of the oxygen from the greater portion of the red cells leads to tissue-asphyxia. If the affected individual does not die, there may result, in addition to the poisoning, severe disturbances of nutrition, occurring especially in the nervous system. The poisoning itself is characterized by headache, tinnitus aurium, vertigo, malaise, vomiting, fainting, convulsions, paralysis, and coma. The blood, as a result of the presence of carbon monoxide, becomes a bright violet or cherry-red color, so that the hyperæmic skin and internal organs also appear bright red.

Hydrocyanic acid (*CNH*) is found in unstable combination in the leaves, bark, and seeds of many plants (bitter almonds, cherry- and peach-stones, apple-seeds, leaves of the laurel, bark of *Prunus padus*, tubers of many of the Euphorbiaceæ, flaxseed, etc.). *Potassium cyanide* (*CNK*) is used in many of the technical arts. The action of both

of these poisons upon the blood is the formation of cyanmethæmoglobin, which gives the blood a bright red color and produces a bright red post-mortem lividity.

Hydrogen sulphide (H_2S) is a constituent of the gas of sewers and dung-pits. When inhaled in large amounts, it may cause sudden death from paralysis of the nervous system. When hydrogen sulphide is for some time brought into contact with blood containing oxygen (as is usually the case in decomposing cadavers), a sulphur-methæmoglobin is formed, which gives to the blood a greenish color.

The poisons that dissolve the red blood-cells, in part with the formation of methæmoglobin, belong partly to the oxidizing substances (ozone, iodine, sodium hypochloride, chlorates, nitrites, and nitrates); partly to the reducing agents (nascent hydrogen, palladium hydride, pyrogallol, pyrocatechin, hydrochinon, and alloxanthin); also and partly to substances which have neither a reducing nor oxidizing action (salts of aniline and toluidin, acetanilid). In the transformation of hæmoglobin into methæmoglobin through oxidizing substances, oxyhæmoglobin is present as an intermediate stage.

The formation of methæmoglobin can occur either in the red blood-cells or in the hæmoglobin which has escaped into the blood-plasma; but the destruction of the blood-cells and the escape of hæmoglobin into the plasma are not always followed by the formation of methæmoglobin. In the case of a marked destruction of red cells, as in poisoning from phallin, helvellic acid, arseniuretted hydrogen, only a portion of the hæmoglobin is changed into methæmoglobin. Hæmoglobin and oxyhæmoglobin have a red color, methæmoglobin a sepia-brown.

Dissolution of the red blood-cells and the formation of methæmoglobin occur in the case of a part of those poisons causing local tissue-changes, as in poisoning with acids, metallic salts, phosphorus, arsenic, and snake-venom.

Very large doses of *potassium chlorate* (ClO_3K) may cause death in a few hours through the destruction of red blood-cells and the action of the potassium, with the occurrence of vomiting, diarrhœa, dyspnœa, cyanosis, and cardiac insufficiency. The blood becomes chocolate-brown in color. In more protracted cases of poisoning through smaller doses, products of blood destruction are found in the spleen, liver, bone-marrow, and kidneys; and the urine may show a brown-red to black color (methæmoglobin). Delirium, numbness, coma, and convulsions occur during the course of the intoxication, showing that the central nervous system suffers severely. *Pyrogallol* ($C_6H_3[OH]_3$) produces similar effects; hydrazin ($H_2N—NH_2$) and *phenylhydrazin* cause, in addition to hæmolysis and the formation of methæmoglobin, multiple thromboses. In poisoning with *toluylendiamin* ($C_6H_3[NH_2]_2CH_3$) the chief action is the destruction of red blood-cells leading to deposits of iron-containing pigment in the spleen, liver, and bone-marrow. In cats methæmoglobin may be excreted through the urine (*Biondi*). In poisoning with *picric acid* ($C_6H_2[NO_2]_3OH$) there occurs, in addition to the blood changes and the formation of methæmoglobin, a severe irritation of the central nervous system finding expression in violent convulsions. *Aniline* ($C_6H_5NH_2$) acts in a similar manner, and *carbon bisulphide* (CS_2) not only produces changes in the blood but also irritates and causes paralysis of the central nervous system.

According to Kobert, *ricin* derived from the seeds of the castor-bean, and *abrin* from the seeds of *abrus precatorius*, should be classed with the blood-poisons, in that in the test-tube they cause an agglutination of the red cells and the formation of a flocculent precipitate. In animals poisoned experimentally, local irritations, tissue-degenerations and inflammations, similar to those caused by certain bacterial toxins, are produced, as well as disturbances in the centres of the medulla oblongata, leading to cessation of respiration with progressive falling of blood-pressure. Tissue-degenerations, inflammation, and hæmorrhage are found, after longer action, at the point of application and in the intestine, where the poison is excreted. Degenerative changes are also found in lymphocytes, liver and kidney cells, and heart muscle.

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§ 9. The last group of poisons, generally classed together as **nerve** and **heart poisons**, is characterized chiefly by the fact that, in spite of the severity of the symptoms, as shown in the form of irritations and paralyses, anatomical changes either cannot be recognized at all or are confined to structural changes in the protoplasm of individual nerve-cells, which are of similar character in the case of different poisons. This is especially the case when the poison is quickly fatal, while if the poisoning runs a protracted course, or in the case of chronic poisoning from small doses, extending over months and years, there are very often found marked anatomical changes—a fact which may be taken as evidence that these poisons do not produce solely functional disturbances of the nervous system, but cause injury to the cell-protoplasm which may be manifested in the form of degenerations.

Of the very great number of *poisons which act especially upon the nervous system* and may cause death through its paralysis, the most important are: chloroform, chloral hydrate, alcohol, ether, opium and its alkaloid morphine, cocaine, atropine, hyoscyamine, daturine (stramoni-

um-atropine), nicotine, coniine, cicutoxin, santonin, quinine, veratrine, colchicine, aconitine, strychnine, cytisin, curarine, and samandarine (salamander-poison).

Of the *heart-poisons*, digitalin, helleborin, muscarine, and phrynin (poison of toads) are of special importance.

Chloroform ($CHCl_3$), when applied directly to the mucous membranes, causes local irritation and may produce transitory inflammation. When conveyed to the blood through inhalation or by absorption from the intestinal tract, it gives rise, after a short period of stimulation, to a condition of diminished irritability of the cerebral gray and white matter. According to *Binz*, the protoplasm of the ganglion-cells suffers a slight coagulation. Death may be caused by paralysis of the central nervous system, as well as by a premature heart-failure; the latter, however, occurring only when the heart is abnormally weak or degenerated. Certain individuals show an especial susceptibility to the action of chloroform. The long-continued use of chloroform may cause degenerative changes in different organs, as the heart, kidneys, liver, muscles, and blood.

Ether (*diethyl ether* $C_2H_5OC_2H_5$) acts similarly to chloroform, but is less poisonous, and acts less detrimentally upon the heart.

Nitrous oxide (N_2O) acts chiefly upon the cerebrum, lowers the sensibility of pain, and paralyzes consciousness; later, the action may extend to the spinal cord, the medulla oblongata, and the heart.

Alcohol (C_2H_5OH), after a transitory stimulation, has a depressing and paralyzing action upon the brain, at the same time causing a dilatation of the arteries of the skin, so that in intoxicated individuals severe chilling through the skin may easily occur. Death may take place suddenly, with symptoms similar to those of apoplexy; more frequently there is a gradual loss of consciousness and of sensory perception, the respiration becomes slower, the pulse small, the face cyanotic; complete coma and general paralysis forming the closing symptoms. The immoderate use of alcohol for months or years may cause degenerative atrophies of liver and kidneys associated with increase of connective tissue; further, sclerosis and atheroma of the arteries, degeneration of the brain, etc., are ascribed to the action of alcohol. At the present time it is impossible to say in what manner, how often, and to what extent these changes are dependent upon the use of alcohol. Much is ascribed to the action of alcohol that is not in any way caused by it and is due wholly to the action of other injurious agents. It is certain, however, that drunkards suffer frequently from disturbances of digestion and circulation, catarrhal inflammations of pharynx, larynx, and bronchi, and disturbances of cerebral function; and that the disease of the brain known as delirium tremens, which is characterized by general muscular tremors, obstinate insomnia, anxiety, and hallucinations, is especially to be ascribed to alcoholism.

Chloral hydrate ($CCl_3CHO.H_2O$) causes local irritation of mucous membranes, and through the blood produces paralysis of the brain, spinal cord, and heart, and thus induces sleep. In fatal doses, death follows deep coma as a result of œdema of the lungs due to the general relaxation of the tissues.

Opium and *Morphine* ($C_{17}H_{19}NO_3$) depress the cerebral functions, thereby inducing sleep; in individual cases there may be a preceding period of stimulation. Large doses lead to unconsciousness, paralysis of muscles, slowing and weakening of the heart's action, contraction of the pupils, slowing of intestinal peristalsis, diminution in the exchange of gases in the blood dependent upon diminished excitability of the respiratory centre. There is no characteristic autopsy finding; the blood is usually dark and fluid. The chronic use of opium may give rise to digestive disturbances, emaciation, vertigo, sleeplessness, neuralgias, imbecility, impotence, weakness of the bladder, hallucination, tremors of the hands and feet, fever, etc., yet these symptoms may vary much in different individuals. In chronic morphinism the organism becomes accustomed to increasingly larger doses; withdrawal of the drug causes severe nervous disturbances, and under certain conditions dangerous collapse.

Cocaine ($C_{17}H_{21}NO_4$) produces peripherally a dulling of the excitability of the sensory nerve-endings; centrally, first a stimulation and later a paralysis. The chronic use of cocaine gives rise to symptoms similar to those of chronic morphinism.

Atropine and *hyoscyamine* ($C_{17}H_{23}NO_3$), the alkaloids which are found in the Solanaceæ (deadly nightshade, thornapple, and henbane), cause paralysis of the peripheral nerve-organs and a central stimulation, followed later by paralysis. Solutions of atropine introduced into the eye produce dilatation of the pupil and paralysis of accommodation for near vision, through its paralyzing action on the endings of the motor oculi in the iris. Atropine may further cause suppression of the secretion of certain glands (as the submaxillary); it also inhibits intestinal peristalsis. As a result of the action of this poison upon the brain, a condition of excitement, gayety, inclination to

laugh, leading even to insanity and frenzy, may be produced, followed by paralysis. The autopsy findings are negative.

Nicotine ($C_{10}H_{14}N_2$), a volatile alkaloid found in the tobacco plant, acts upon both peripheral and central nervous systems, causing nausea, salivation, vomiting, diarrhœa, vertigo, muscle-weakness, headache, convulsions, delirium, and paralysis. Chronic nicotine poisoning may give rise to nervous affections and disturbances of the heart's action.

Coniine ($C_8H_{17}N$), the alkaloid present in hemlock, causes paralysis of the peripheral motor nerve-endings, first stimulating and then paralyzing the central nervous system. *Cicutoxin*, a poisonous resin obtained from the water-hemlock (*Cicuta virosa*) produces nausea, vomiting, attacks of colic, cardiac palpitation, convulsions, and unconsciousness.

Santonin ($C_{15}H_{18}O_3$) causes convulsions by its action on the brain and spinal cord, with benumbing of the sensorium, vertigo, vomiting, salivation, and yellow vision or xanthopsia, in which white is seen as yellow and blue as green.

Quinine ($C_{20}H_{24}N_2O_2$), the most important of the numerous alkaloids contained in the bark of cinchona and other closely related plants, has a paralyzing action upon living protoplasm, and in relatively small doses lowers the functional capacity of the brain. Large doses produce death through paralysis of the centre of respiration and of the heart.

Aconitine, *colchicine*, and *veratrine* produce local irritations and, later, benumbing of the peripheral endings of the sensory nerves. On the central nervous system they have first a stimulating action, later a paralyzing.

Strychnine ($C_{21}H_{22}N_2O_2$), obtained chiefly from the plant nux vomica, causes an increased reflex excitability of the nerve centres, so that the slightest external stimulus may produce tetanic convulsions. Death may occur in from ten to thirty minutes after the first convulsion, and is the result of central paralysis, namely, of the vasomotor centre.

Curarine ($C_{18}H_{35}N$), the active principle of the arrow-poison curare, is probably derived from the cortical portion of the roots of different plants of the strychnia family. When used in small doses it paralyzes the endings of the motor nerves of the muscles. Larger doses cause paralysis of the central nervous system and of the vasomotor nerves, after a temporary stimulation.

Digitalin and *digitalein*, two glucosides obtained from the foxglove, act as local irritants; after absorption they stimulate the heart, vagus-centre, and the musculature of the blood-vessels, so that with a slowing of the heart-beats there is an increase of blood-pressure. Large doses cause headache, delirium, tinnitus aurium, irregular increase in the frequency of the heart's action, convulsions, and coma.

Helleborin, a glucoside obtained from hellebore, acts similarly to the preparations of digitalis.

Muscarine ($C_5H_{15}NO_3$), the poison of the fly-agaric, acts as a stimulant to those nerve-endings which are paralyzed by atropine. The intense excitation of the inhibitory centres of the heart causes stoppage of the unparalyzed heart, and death is thereby produced. The general symptoms of muscarine poisoning are salivation, vertigo, anxiety, nausea, vomiting, diarrhœa, convulsions, and finally unconsciousness. Small doses produce a condition of excitation similar to that of drunkenness.

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4. *Origin of Disease through Infection or Parasitism.*

§ 10. *The entrance of living organisms from the outer world into the tissues of the human or animal body, and their multiplication there with the production of pathological processes,* is known as **infection.** Since these organisms take their food from the tissues, they are during their stay in man or in animals to be regarded as parasites, and therefore the affections known as the **infectious** diseases are nothing more than **parasitic conditions.**

The parasites causing the majority of the infectious diseases are now known. In those diseases in which they are not yet discovered (smallpox, measles, scarlatina, etc.) the existence of a parasite may be assumed through the **peculiarity of the infectious disease**; and, indeed, through the fact that for infection only the smallest imponderable amount of infective material is necessary, so that the severity of the disease can be explained only through the assumption of an increase of the harmful agent within the body; and, further, through the fact that the disease in question is characterized by definite, constantly recurring phenomena and by a typical course. It may happen that a given disease may spread from one affected individual to other individuals, giving rise to a **pestilence** or **epidemic,** which may spread throughout one house or city or throughout the whole land or over many lands. The spread of the disease occurs sometimes in such a way that one gets the impression that there is a direct passage from man to man, a **direct contagion** (diphtheria, smallpox, measles, influenza, whooping-cough, gonorrhœa, syphilis, and leprosy); at other times, as if the causal agent of the disease clung to certain regions as a so-called **miasma** (malaria), and from thence infected the individuals who came into its neighborhood; finally, at other times, as if the disease had been spread through an affected individual, who had acquired the disease somewhere and had then changed his residence and had infected the new place of residence in some way or other, so that the inhabitants there acquired the disease. Infections that may be spread by this last method may be designated **miasmatic contagious diseases** (Asiatic cholera, yellow fever, typhoid).

The parasites that cause the infectious diseases belong, according to our present knowledge, for the greater part to the **schizomycetes** or **bacteria;** but certain of the higher plants, the **mould-fungi** (eumy-

cetes), and the **yeasts** may also cause infectious diseases. Further, the **animal parasites** are also represented by numerous species, belonging in part to the **protozoa,** in part to the **worms,** and partly to the **arthropoda.** It has been the custom to accord to the animal parasites an especial position, since many of them do not increase in the host in whom they live, but pass only through certain stages of development without causing such symptoms as are characteristic of the infectious diseases. Such a distinction will not hold good, since typical infectious diseases (malaria) may also be caused by animal parasites. Further, in the case of many of the animal parasites a definite increase does take place within the human organism.

With the recognition that the infectious diseases are caused through the parasitism of minute living-*microörganisms* not visible to the naked eye, the view was soon reached that pure contagious diseases must be caused by parasites that could thrive only within the human or animal organisms; while miasmatic diseases arose through living agents which occur in the outer world and occasionally gain entrance into man or animals. In the first case the microörganisms were designated *endogenous parasites,* in the second *ectogenous.* It was assumed in regard to the miasmatic contagious diseases that the microörganisms could increase either within the body or in the outer world; but, in the latter place, only when they passed from the human or animal body into water, food, or earth.

With certain limitations this view is still to-day regarded as correct; but, according to later experiences, its original application is not always correct, since many microörganisms that ordinarily increase only in living tissues as parasites require for their growth outside of the human body certain conditions of life that make their multiplication possible, so that in a certain sense a contagium may become a miasma. The causal agents of measles, scarlatina, and of syphilis can develop only inside of the human body; that of smallpox, within the body of man and cattle, and we have not yet succeeded in growing them in artificial media. Tubercle bacilli ordinarily develop only in the tissues of man and different vertebrates; but they may be cultivated on certain media at the temperature of the body, and subsequently can be successfully inoculated into man and animals. Staphylococci and streptococci, which produce suppurations, anthrax bacilli, typhoid bacilli, cholera spirilla, and others grow easily in very different solid and fluid media and can after such an artificial cultivation cause disease in man, both through contagion and through transmission from the outer world. But it should be noted that, even in the last-named cases, the bacteria concerned have often not increased in the outer world, so that, for example, water used for drinking becomes only the conveyer of the infective agent.

Malaria, which is considered the chief type of a miasmatic disease, is produced by a microörganism, which, outside of the human body, must pass through definite stages of development in certain mosquitoes or it will die. Through the taking up of blood from a malarial patient the infected mosquitoes (different forms of Anopheles) represent the malaria-producing miasm, and man is again infected through their bite, and not, as was originally supposed, through mists arising from marshes or through bacteria. It is also possible to produce an infection with malaria by the transfusion of blood from a malarial patient to a healthy individual.

The view that certain diseases, particularly **epidemics,** were of parasitic origin, is very old, and found expression in the works of *Kirchner* (1602–1680), *Lancisi* (1654–

1720), *Linné* (1707–1778), and others. It has been left to very recent times, however, to place the theory of the parasitic nature of the infectious diseases upon a secure foundation. Though several decades ago *Henle*, *Liebermeister*, and others asserted that the peculiarities of infectious diseases could be explained only by the assumption of a *contagium animatum*, the establishment of this doctrine is due to the results of the investigations of the last thirty years.

The **climate** is often held responsible for the origin of disease, and we are inclined to consider a region having a uniform temperature, much sun, and little wind as a healthy one, while one having marked variations of temperature, abundant precipitation, little sun, and much wind is regarded as unhealthy. This is true to a certain extent, in so far as invalids or individuals susceptible to the influences of weather are concerned, but a much more important and decisive criterion of the healthfulness of a region is the presence or absence of specific agents of disease, vegetable or animal parasites that may infect man. Such disease-producing agents may exist in affected members of the population of the region, in the drinking-water, in the earth, or in animals etc. In the tropics the malarial parasites play the most important rôle, their transmission to man being brought about through the agency of mosquitoes. Therefore, the most beautiful region which seems to offer the best climate may be unhealthy; while raw, cold, and inhospitable regions may be very healthy through the absence in them of the causal agents of disease.

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See also § 12.

§ 11. The **bacteria** are small, unicellular organisms, which appear in the form of little spheres (cocci), and fine, straight, or curved rods (bacilli and spirilla), frequently uniting in peculiar combinations. Many possess motile organs in the form of flagella. Under especial

conditions some of them produce spores or peculiar permanent forms, mostly oval in shape.

From the standpoint of the physician bacteria may be divided into the **non-pathogenic** and the **pathogenic.** To the latter belong all those that are able to increase in the human and animal organism. But this classification is not altogether satisfactory, inasmuch as pathological conditions may be caused by bacteria that are not able to increase within living tissues. This rests upon the fact that all bacteria, not only the pathogenic, but also the non-pathogenic, in their growth in nutritive media (albumin, peptone, gelatin, non-nitrogenous media), decompose these, and thereby often produce **substances that are toxic** for man and for the higher animals. These changes in the nutritive media are brought about chiefly by the action of *ferments* and *enzymes*, the latter process being regarded as a direct function of the living cell substance, while the former is due to the action of ferments or enzymes that are liberated from the cells.

The most important of the substances produced by the decomposition of proteids are the nitrogenous basic **cadaveric alkaloids** or **ptomaïns, many of which are poisons for man.** For example, the toxic products neuridin, cadaverin, putrescin, neurin, and methylguanidin, the last three of which are poisons, may be obtained in pure form from decomposing meat. If these enter with the food into the human body **symptoms of intoxication** may be produced without any development of bacteria in living tissue. On the whole, their activity is not considered very great, and it is questionable whether the artificially produced poisonous ptomaïns ever arise during the processes of decomposition.

Besides the property of producing ptomaïns and other poisonous substances (for example, hydrogen sulphide), which belongs to many different bacteria, the **pathogenic bacteria** produce **other poisons specific for the individual species.** The first of these to be considered are the **toxins** in the narrower sense, that is, poisonous substances which do not belong to the ptomaïns and are also not albuminous bodies (toxalbumins). They are the products of secretion of the bacterial cells and can be separated by filtration from the bacteria. The most important representatives of such poisons are those produced by the *bacilli of diphtheria* and *tetanus*, both in cultures and in the human organism. It is probable also that cholera spirilla produce them in small amount. The toxins are very unstable bodies and quickly lose their activity through heating above 50° C., the effect of light, and through the action of acids and other chemical substances; when dry they will stand 100° C. without injury. Their chemical structure is not known; they may be compared with the enzymes. Their activity is also limited to the animal susceptible to the given disease. When injected into susceptible animals, their action takes place after a *period of incubation* known as the *period of latency*. In the affected organism they cause the production of *antibodies* or *antitoxins*, which render the toxin harmless in the organism and also neutralize it *in vitro*.

As a second form of specific poison there occur **intracellular toxins** or **endotoxins,** that is, poisons which cling to the bacterial cell and are separated from it only with difficulty. Even less is known of their nature than of the true toxins. Typhoid bacilli, cholera spirilla, and pneumococci form such poisons, and it has been assumed that they become active after the destruction of the bacteria in the human organism.

A third form of bacterial poison is found in the **bacterial proteins or**

micoproteins, that is, the substance of the bacterial cell itself. They produce chiefly a local effect, finding expression in inflammatory processes. It is very probable that such a local action occurs in all bacterial infections in which the bacteria develop locally. If the bacteria concerned produce antitoxins the action of these is combined with that of the bacterial proteins.

In individual cases it is very often impossible to decide to what extent ptomaïns or to what extent specific bacterial toxins and micoproteins are concerned in the production of the pathological condition. The term **bacterial toxin** is very often used in a broad way to cover all of the poisonous substances produced by bacteria.

Some **pathogenic bacteria** increase first in the *outer world* (for example, the tetanus bacillus), and only occasionally do they develop in the human or animal body; on the other hand, other forms develop *ordinarily only in the human or animal organism* (tubercle bacilli, glanders, leprosy, diphtheria, and influenza bacilli) and need for their development outside of the body especial nutritive media, or, indeed, they cannot be cultivated at all. *Others still increase with especial energy in human and animal tissue, but are also easily grown upon different nutritive media* (streptococcus, staphylococcus, anthrax bacillus, typhoid bacillus, cholera spirillum), and are also able to multiply under natural conditions in the outer world.

The distribution of pathogenic bacteria from the affected individual to the outer world takes place through coughing, sneezing, expectoration, speaking, through intestinal and urinary discharges, secretion from wounds, sloughing of portions of tissue, etc. When thrown out into the air they may remain floating for some time and be carried to some distance, but, sooner or later, they become attached to some object. Through drying and through sunlight many of them are quickly destroyed. Others remain alive for a certain period, often a very long time, especially in the form of spores, and may be found in either a dry or moist state, in the water or in the earth. If they find the proper food-material and if the temperature is high enough for their development, the bacteria may multiply.

From the place where they are thrown down, or from the objects to which they cling, or where they have undergone further development, the bacteria may later suffer a wider distribution. Stronger currents of air may carry them farther away, especially from the objects to which they simply cling, or also in the dust of the room or of the street. Many of them are brought to the human and animal organism partly through food and drink, partly through the air, and partly through contaminations of the fingers.

The **avenues of entrance for bacteria** are, in general, the mucous membranes of the intestinal canal, respiratory tract, and the middle ear, the conjunctiva, the alveoli of the lungs, and open wounds. But it should be noted that many bacteria are able to gain an entrance only in certain tissues, for example, the typhoid bacillus and the cholera spirillum gain entrance only from the intestine and not from the skin or lung. Through recent wounds, both pathogenic and non-pathogenic bacteria are rapidly taken up into the lymph and blood; while through wounds showing healthy, granulating, uninjured surfaces, the entrance of many bacteria into the tissues is hindered. Pathogenic bacteria (pus cocci) not infrequently enter through the uninjured skin, either by way of the hair-follicles or through the sebaceous or sweat-glands. Under especial

conditions (coitus, surgical operations, dribbling of urine, childbirth) the infection may take its start from the mucous membranes of the urogenital tract. Some infections may be transmitted by insects, which have taken up bacteria with the blood or secretions of a diseased individual or animal, or, having become contaminated externally by such, may infect an open wound by scraping the bacteria off their legs upon the exposed surface, or by the direct introduction of germs into the skin or accessible mucous membranes during the act of stinging or sucking. If meat containing bacteria be eaten, and if the animal while alive was affected by an infectious disease which also occurs in man, this particular disease may be transmitted to man, in case the bacteria had not been previously destroyed.

Bacteria arrive at the point of entrance, sometimes in association with chemically active substances, sometimes without such; the first is more likely to occur in the intestinal tract, the second in the respiratory passages and in the lungs; yet chemical substances may also find their way into the lungs with bacteria, and bacteria may enter the intestinal canal without the association of chemically active material.

If **toxic bacterial products** enter in considerable amount into the intestinal canal or wounds at the same time with the bacteria, the symptoms of an **intoxication** may be produced without an infection, that is, without an increase of the bacteria in the tissue taking place. This event may also happen when bacteria producing such poisons develop in the contents of the intestine, in wound-secretions or in necrotic lung tissue, and increase there as *saprophytes*. Strictly speaking, we cannot regard this as an infection, but must look upon the disease so produced as an **intoxication**; but it is not always possible in such cases to draw a sharp line between an intoxication and an infection, since bacteria originally developing as parasites not infrequently penetrate into the tissues and there multiply.

Intestinal intoxications dependent upon bacterial toxins occur especially when meat or fluids in a condition of bacterial decomposition have been eaten as food. To such intoxications belong a large proportion of the affections designated as *meat-*, *sausage-*, *fish-*, and *cheese-poisoning*, in which the poison is either taken as such into the intestinal canal, or first formed there. Likewise, many vegetables in a condition of fermentation and decomposition, for example, cabbage, peas, beans, corn, rice, etc., exert a harmful influence upon the intestine or upon the entire organism, especially when they have been eaten in large amounts or for a long period of time. Nor infrequently there occur also acute poisonings of the same kind.

If the bacteria which have entered the body through one of the above-mentioned avenues of infection are in a strict sense pathogenic, so that they give rise to an **infection**, they may increase first at the point of entrance, in the intestinal mucous membrane, in a wound, in the skin, etc. The **local effects** of their growth are dependent primarily upon the individual characteristics of the bacteria, as well as upon the peculiarities of the affected tissue. In general, the local action is characterized by tissue-degenerations, necrosis, inflammations, and new-formation of tissue, so that it is possible in many cases to determine the nature of the infection, that is, the species of bacteria causing the infection, from the character of the local changes. It is, however, difficult or impossible to determine in every case the exact mode of action of the multiplying bacteria; in general, it mav be said that the

processes of chemical metamorphosis excited by the multiplication of the bacteria produce certain changes in the tissue-cells, in that different substances of active chemical nature either kill the cells, or at least induce degenerative changes in them, or in part excite increased cell-activity. In the further development of the process the substances derived from dead and dissolving bacteria may also produce effects upon the surrounding tissue. In a certain sense, therefore, there occurs through the local growth of bacteria a *local intoxication*, which is of far greater significance than the *withdrawal of nutritive material* through the consumption by the bacteria of food substances. The latter is, however, not wholly without significance, inasmuch as the chemical changes produced by the bacteria in the tissue juices often render these unfit for the nourishment of the tissue-cells, so that the cells suffer even when no poisonous substances are produced.

The **participation of the entire organism** in a local bacterial infection may be very slight or wholly absent, so that the disease appears as a purely local affection (tuberculosis). In other cases the toxins and toxalbumins formed in the local focus of infection are absorbed into the body fluids (i.e., into the blood), and a **general intoxication** (*toxinæmia*) is produced; that is, poisonous effects are exerted upon the nervous system, sometimes upon the blood itself and upon the heart; and the poisons thus taken into the body may produce demonstrable changes in the internal organs, particularly in the excretory glands, at times also in the skin. In many diseases (tetanus, typhoid fever, streptococcus and staphylococcus infection, diphtheria) the symptoms of poisoning are especially prominent.

If healing does not take place in the primary seat of infection, the neighboring tissues may be involved by an **invasion of bacteria by continuity.** Very often the **bacteria gain entrance to the lymph-vessels or blood-channels** (*bacteriæmia*), and in this way are transported and spread over the entire body. The result of this *metastasis of bacteria* is the production of a **lymphogenous** or **hæmatogenous infection**; that is, secondary *foci* of disease *identical in character with the primary seat of infection* are formed at a distance from the primary focus. In certain diseases (tuberculosis, suppurations, plague) the number of **metastases** is usually very great, so that many parts of the body (lymph-glands, liver, lung, brain, muscles, bones, kidneys, etc.) may contain diseased foci. On the other hand, in other infections metastasis of bacteria from the original focus to other organs does not occur (tetanus, diphtheria), or the transported bacteria cause only changes of a milder type (typhoid fever).

The entrance of bacteria into the blood leads to **bacteriæmia.** During the transportation of bacteria through the blood-vessels, there is usually no increase of the bacteria in the circulating blood, the *blood serving only as a vehicle* to carry the bacteria to other parts of the body, multiplication occurring first at those points where the bacteria have come to rest. Nevertheless, in certain infections (anthrax) the *bacteria increase enormously in the circulating blood*, and in this way may cause damage to the blood itself. Through the obstruction of small blood-vessels by the multiplying bacteria, there may be added to the intoxication also local disturbances of circulation.

The metastasis of bacteria or toxic substances, or both, from a localized seat of infection, and the production thereby of secondary foci and symptoms of intoxication, give rise to the condition which is generally

termed **sepsis.** According to the predominant symptoms there may be distinguished a *septæmia* or *septicæmia*, a *pyæmia* and a *lymphangoitis.* Through the combination of both the latter with septicæmia, *septicopyæmia* is produced. Originally the designation **septicæmia** was applied to those cases in which a localized infection was associated with *intoxication* caused by bacterial poison or a *toxinæmia* without the spread of bacteria through the body. At the present time, according to the precedent set by Koch, Gaffky, and others, septicæmia is used to designate the condition characterized by the entrance of both bacteria and their poisons into the blood, a coincident *toxinæmia* and *bacteriæmia;* indeed, by many authors the pure intoxication or toxinæmia is separated from septicæmia.

The term **pyæmia,** originally signifying a metastasis of pus through the blood, is at present employed to designate the condition in which the metastasis of bacteria gives rise to the formation of *metastatic abscesses.*

In **septicopyæmia** the symptoms of toxinæmia and bacteriæmia are combined with the formation of metastatic foci. **Lymphangoitis** is an *inflammation of the lymph-vessels and their surroundings* caused by transported bacteria.

Sepsis in its different forms is most frequently caused by the true *pyogenic organisms, staphylococcus pyogenes aureus,* and the *streptococcus pyogenes,* but similar conditions also occur in infection with the *pneumococcus, gonococcus, typhoid bacillus, colon bacillus, plague bacillus,* etc.

If **bacteria** are deposited secondarily in the body-passages which are lined with mucous membrane, as in the respiratory or urogenital tract, **they may multiply within these tracts** and produce their characteristic pathological changes. Likewise, they may **multiply** also **within the large body-cavities,** in the peritoneal, pleural, and subarachnoid spaces. In the case of an infection occurring in a pregnant woman, many varieties of **bacteria** (anthrax, symptomatic anthrax, glanders, recurrent fever, typhoid, pneumonia, the pyogenic bacteria, tuberculosis) may be **transmitted to the fœtus.**

The description given above of the course of an infection may be taken as a general type, and many infections run such a course (typhoid, pyæmia, erysipelas, plague, diphtheria, tetanus, tuberculosis, syphilis, leprosy, glanders, actinomycosis, etc.); but there are also many deviations from this scheme. In the first place, it not infrequently happens that in an infection which in general runs a typical course, the primary seat of infection is not demonstrable, either because no changes occurred at the point of entrance, or the changes produced have since disappeared. Such forms of infection are known as **cryptogenic;** they may be **lymphogenous** or **hæmatogenous.** It is typical of many infections that the primary localization of the cause of the disease is not recognizable, so that *general* symptoms *occur before local changes are demonstrable,* and the tissue-changes occurring later have more the character of a *secondary localization of the poison of the disease.* This occurs especially in a number of infectious diseases, the causes of which are unknown to us; for example, in scarlet fever, smallpox, and measles; yet in many infections whose causes are known we are not always able to discover at what point the first multiplication of the bacteria occurs. Thus we know that in relapsing fever the spirilla are found in the blood in large numbers at the time of the fever, but the place of their multiplication is unknown to us.

Not infrequently a **secondary infection** may be joined to one already present. In many cases the association is entirely accidental, in other cases the anatomical changes produced by the first infection cause a local predisposition to the new invasion. To the first group would belong, for instance, a croupous pneumonia occurring in an individual suffering with tuberculosis of the kidney or bones; while the occurrence of an infection with cocci causing suppuration and septic intoxication during the course of typhoid, influenza, diphtheria, scarlet fever, dysentery, caseous ulcerating tuberculosis, etc., may be regarded as due to the production of local tissue-changes favoring the entrance of bacteria. These secondary infections usually aggravate the sufferings of the patient in that a new independent disease is added to the one already present; but it may also happen that the organisms entering secondarily into the body grow only as saprophytes in exudates or in tissues killed by the first infection. In certain infections, as, for example, in many forms of purulent processes, the tissues may contain, even at an early stage, two or more varieties of bacteria—a **mixed infection** or **double infection.** The associated bacteria can persist in their association and in common excite pathological changes; but they may also become separated from each other, in that one microörganism gains a wider distribution than the other.

It has been known for many years that during decomposition poisonous substances are formed. As early as 1852 *Beck* observed that ammonia hydrothionate, which occurs in pus and putrid ichor, possessed septic properties when injected into animals. *Panum*, in 1863, obtained from decomposing material a *putrid poison*, that is, a body not destroyed by boiling and evaporation, which possessed an action similar to that of snake-poison and the vegetable alkaloids and caused in dogs salivation, dilatation of the pupils, diarrhœa, fever, and severe prostration. *Von Bergmann* and *Schmiedeberg* obtained from decomposing yeast a crystalline body, *sepsin*, which in animals produced the symptoms of a putrid intoxication. *Senator*, *Hiller*, and *Mikulicz* extracted from decaying tissue-masses by means of glycerin a substance which likewise possessed a septic action. *Billroth* called this poisonous substance *putrefactive zymoid*. *Selmi* endeavored to characterize all these substances more minutely, and obtained from different constituents of cadavers extracts, partly soluble in ether, partly in water, which he recognized as fixed bases of alkaloid-like character, and which he designated as **cadaveric alkaloids** or **ptomaïns.** *Gautier*, *Etard*, *Zuelzer*, *Sonnenschein*, *Béchamp*, *Schmiedeberg*, *Harnach*, *v. Nencki*, *Otto*, *Angerer*, and others also found in decomposing tissues similar cadaveric alkaloids, which in experiments upon animals were partly inert, and partly toxic, producing in the latter case symptoms of poisoning similar to curare, morphine, and atropine. To *von Nencki* (1876) is due the honor of being the first to obtain a cadaveric alkaloid in its pure form and to establish its formula: this was accomplished in the case of collidin, obtained from decomposing glue and albumin, its platinum salt crystallizing in flat needles. Following *v. Nencki*, *Etard*, *Gautier*, and *Baumann*, and especially *Brieger*, have studied ptomaïns, the last named having obtained a large number of them in a pure state and determined their physiological action. For instance, *Brieger* obtained from fibrin peptone a poison (peptotoxin) which in animals causes symptoms of paralysis and ultimately death. From decomposing horse-flesh he extracted three substances crystallizing in needles, namely, neuridin, neurin, and cholin, the second of which is markedly poisonous, and, like muscarine, causes salivation, disturbances of circulation and respiration, contraction of the pupils, and clonic convulsions. From fish-flesh he obtained, besides neuridin, three other poisonous bodies: ethylendiamin, a substance similar in its action to muscarine, and a substance called gadinin. From decomposing glue and cheese he obtained the poison neurin, and from decomposed yeast dimethylamin.

The majority of ptomaïns are not found in fresh tissues, and it is therefore very probable that they are derived from the splitting of chemical combinations present in the tissues. Thus it is probable that cholin is formed from the splitting of lecithin, and by the further decomposition of cholin the poison neurin is formed. Cholin and neuridin are, according to *Brieger*, demonstrable even in the fresh human brain.

After the poisonous nature of part of the ptomaïns had been made known through the researches mentioned above, there was developed the *hypothesis* that the toxic symptoms observed in infectious diseases could be entirely, or in a great measure, ascribed

to the action of the toxic ptomaïns. Through the investigations of recent years (*Roux, Yersin, Buchner, Brieger, C. Fraenkel, Pfeiffer, Ehrlich, Wassermann*, and others) it has been shown that besides the ptomaïns there occur **specific bacterial poisons,** which are characteristic for the given bacterial species. These were first regarded as active albumin bodies and were called **toxalbumins.** *Brieger* and *Fraenkel* hold the view that they are formed by the action of bacteria from the albumins of the body juices. *Buchner*, on the contrary, believes that they are produced by the bacterial cell itself. Investigations on the poisons formed in diphtheria, tetanus, cholera, typhoid fever, pneumonia, and tuberculosis have shown that the so-called toxalbumins are not albumin bodies, and have led to the differentiation of different poisonous substances as given in the text above.

The **toxins,** in the strict sense, may be compared, according to their origin, with the **enzymes** formed by the body cells (pepsin, trypsin, ptyalin) which produce hydrolytic splitting. On the other hand, the **endotoxins** clinging to the cells may be compared with the expressed juice of yeast known as **zymase** (*Buchner*), which is able, in the same way as the living protoplasm of the yeast-cell, to excite an alcoholic fermentation in fluids containing sugar. Toxins and enzymes are mixed with albuminous substances which up to the present time have not been separated from them. This explains why they were earlier regarded as albuminous bodies. *Brieger*, who first characterized the toxic substances as toxalbumins, has himself prepared toxins that gave no albumin reaction.

According to the views of Ehrlich, only those substances are **poisons** that possess a chemical affinity for some element of the body and through their union with this cause an injurious action that may be recognized clinically (toxophorous affinity). A **toxin** or **haptin** is, according to him, a poison which possesses *two specific atomic groups*, a *haptophore group* which permits the union with the body cells through the *haptophorous group* of the latter, and a *toxophore group* which exerts the poisonous action. If in any poison the specific action of the toxophore group is lost, while the haptophore group remains, there arise **toxoids** or **non-poisonous haptins** which may anchor themselves to the body cells but are no longer poisons. Finally, there occur also primary bacterial products (in diphtheria), the **toxons** (*Ehrlich*), that is, poisons which have the same haptophore group as toxins but a less active toxophore group.

Since the *intracellular toxins*, the **endotoxins** (typhoid bacilli, cholera spirilla, B. pyocyaneus, pus cocci), are stored up in the bodies of the bacteria, the bacterial cell-substance is the most active. In old cultures the poisons pass over into the fluid, but they probably no longer represent the primary endotoxin, but a modification of the same.

Cholera spirilla, typhoid bacilli, and pneumococci form endotoxins, which on the death of the bacteria are in part set free, and become active as such, or act in a modified form at the same time with the **bacterial proteins.**

Anthrax and tubercle bacilli probably form no true toxins, but contain poisons of another kind whose action is combined with that of the bacterial proteins.

The importance and the course of an infection depend, therefore, upon the character of the cells possessing receptors for the given toxin. In tetanus it is the nerve-cell; in diphtheria and tuberculosis the connective-tissue cell. Diphtheria poison does not injure the skin of the mouse, while the one-hundredth or one-thousandth part of the same dose will produce tissue-necrosis in the guinea-pig (*Ehrlich*).

Aggressins: When bacteria are grown in the pleural or peritoneal cavities, in pleural or peritoneal exudates, blood-serum, or even in distilled water, there is formed a substance which, when the non-toxic sterilized culture fluid is inoculated at the same time with a sublethal dose of the bacteria, neutralizes the protective powers of the body and permits the growth of the bacteria. These substances have been called *aggressins*, and may be regarded as serving the bacterial organism in the same way that the opsonins protect the animal body. (*Bail: Arch. f. Hyg.*, 1905.)

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See also § 6 and § 10.

§ 12. The **pathogenic moulds (eumycetes) and the budding fungi** belong, as do the schizomycetes, to the non-chlorophyllaceous thallophytes. They occur in the human organism in the form of jointed or non-jointed and sometimes branching threads or *hyphæ*, and short oval cells, the so-called *conidia*. The eumycetes may be divided into the moulds, the fungus of thrush, and the cutaneous mould-fungi. At times they form fructification organs of peculiar structure. The single cells are much larger than those of the schizomycetes, so that they may be

seen with lower magnifying power. Outside of the body the *moulds* develop as velvety films of different colors, on the surface of many organic substances and fluids, from the carbon-compounds and salts of which they derive their nourishment. The *yeast-fungi* are found chiefly in fluids containing sugar, and are the cause of the alcoholic fermentation of the same.

The spores or conidia, which represent resistant reproductive cells, are for the greater part formed in special organs of fructification, but may also be developed by a simple process of constriction of the ends of the hyphæ, and pass into the air from the surface of the mould-film, and may be widely scattered by the air-currents. Likewise, yeast-cells may be carried about in the air, in the case of the evaporation of a fermenting fluid and the conversion of its residue into dust.

The moulds may, as do the bacteria, *produce poisonous substances in the nutritive media in which they multiply,* usually first outside of the human body, and when these are taken in with the food **symptoms of intoxication** are produced. For example, the chronic disease, known as *pellagra* or *maidism,* which occurs particularly in Italy, Spain, southwestern portion of France, and Roumania, and is characterized by gastro-intestinal disturbances, changes in the skin, spinal and cerebral functional disturbances, and general marasmus, is, according to the view of many writers, the result of the eating of corn which has been spoiled through the growth of *Aspergillus fumigatus* and *flavescens* or *Penicillium glaucum.* According to Ceni the active poisonous substances are produced in the spores of the fungi.

As parasitic agents causing disease the moulds and the yeasts cause only *local infections* characterized by tissue degeneration and inflammation.

The *moulds* develop in regions accessible from without, in the skin, the ear, mouth cavity, lungs, etc. They usually occur first as saprophytes in cerumen, necrotic lung tissue, etc., but they may also penetrate into living tissue.

The *thrush fungus* occurs chiefly in the epithelium of the upper layer of the mucosa of the alimentary tract, but often penetrates into the connective tissue and causes inflammation. Hæmatogenous metastasis is rare.

The *cutaneous moulds* multiply in the epithelium of the skin and cause inflammation (favus, herpes tonsurans, pityriasis versicolor, erythrasma).

The *yeast fungi* develop most frequently in the stomach, particularly after the eating of fermenting fruit juices. In cases of glycosuria they may multiply in the urinary bladder and excite there a fermentation. Within the tissues they develop only rarely, and cause there local inflammations of varying character.

Yeast-like budding fungi occur also in a granulomatous and suppurative process affecting the skin and internal organs (blastomycetic dermatitis, blastomycosis, saccharomycosis, coccidioidal granuloma, etc.). The majority of the cases have occurred in America. The parasites involved cannot at present be definitely classified. By some writers (*Ricketts*) they are believed to belong to the genus Oïdium (*oidiomycosis*). Blastomycetes are supposed to be the cause of a peculiar suppurative disease in horses.

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§ 13. The **production of disease by animal parasites** is most frequently brought about by the introduction of mature parasites, larvæ, or eggs into the intestinal tract through the medium of the food and drink or by unclean fingers. This is particularly true of those parasites whose habitat is in the intestine or the tissues located within the body; such parasites are accordingly designated as *Entozoa.* Parasites living in the outer tissues, as the skin, are termed *Epizoa;* they remain either on the surface of the skin or penetrate into the same from without. The passage of parasites from the intestine into the internal tissues and the changes thereby produced constitute the condition which is usually called, after the designation first used by Heller, an *invasion-disease.* The animal parasites for the greater part produce only local changes, but they can also cause symptoms of a general disease, particularly when the parasites increase in the body and are present in great numbers in the blood or certain tissues, or when they produce toxic substances.

The **parasitic protozoa** are partly harmless parasites, which develop in the secretions of the mucous membranes without causing pathological changes. Other forms, on the contrary, can penetrate into the living tissues, increase inside of cells, and give rise to local morbid changes, characterized chiefly by peculiar new-formations of tissue (coccidia-disease of the rabbit's liver, epithelioma contagiosum). Certain forms, which are probably to be classed as Sporozoa, increase in the blood, as inhabitants and destroyers of the red blood cells, and are the cause of the infectious disease known as malaria. Others still (trypanosomata) inhabit the blood-plasma. It is not impossible that other infectious diseases, for example, small-pox, are caused by parasites belonging to the Protozoa.

The **parasitic worms** (*Nematodes, Cestodes, Trematodes*) occur in man, partly in the adult and fully developed sexual state, and partly in the larval state. In the first case they are for the greater part intestinal parasites, which obtain nourishment from the intestinal contents, rarely sucking the blood from the intestinal mucosa. Fully developed worms are also found in other regions, as in the blood- and lymph-vessels, bile passages, lung, pelvis of the kidney, and in the skin. The eggs or fully developed larvæ produced in the body by parasitic worms are either cast out with the dejecta or, through active wandering or metastasis through the blood or lymph, finally reach other organs of the body, where they pass the first stage of their development. Here they remain, however,

in a larval condition, and do not reach sexual maturity. The larvæ are capable of further development only when they have been taken into a new host, or have been again eaten by the same host.

The worms which reach their sexual maturity in the human body are taken in as larvæ through the food and drink. Their first stage of development is passed in the great majority of cases in animals whose flesh is used for food; in other cases in certain of the lower animals not used as food. Others develop in water or damp earth or even in the human intestine, so that the embryos or eggs, which pass off with the dejecta, develop at once in case they are again introduced into the intestinal tract of man.

The worms which occur in man only in the larval condition (hydatids) develop from eggs which have come from sexually mature worms, which inhabit different animals. They are taken into the intestinal tract usually in the food or drink, but under special conditions eggs capable of development may be contained in the dust of the air, and, being inhaled and finally reaching the intestinal tract, complete the first stage of development.

The intestinal parasites for the greater part produce only slight disturbances, though they may cause mechanical irritation of the intestine. The presence of blood-sucking worms in large numbers (*Anchylostoma duodenale*) can cause anæmia. Some also produce poison (*Bothriocephalus*). Those parasites which enter the tissues may cause in their vicinity mild inflammation and proliferation of tissue, which may produce more marked clinical symptoms when the number of the parasites (*trichina-larvæ*) in the tissues is very great. Others are of pathological importance, in that they reach a large size (*echinococcus cysts*) and thereby crowd aside and compress the neighboring structures.

Otherwise their pathogenic significance depends essentially upon their location. A parasite situated in the muscles or subcutaneous tissue may cause very slight symptoms, while one in the eye, medulla oblongata, heart, or blood-vessels may cause severe disturbances, and under certain conditions death.

The **parasitic arthropoda** (*Arachnida* and *Insects*) come to the human body partly from the outer world, partly from infected animals, and partly from infected human beings. They belong almost wholly to the Epizoa, which have their habitat in and upon the skin and accessible mucous membranes (lice, bedbugs, fleas, mites) or only occasionally take their nourishment from the skin (gnats, gad-flies, flies), a few multiply either in the skin (itch-mite) or upon its surface (lice). Flies and gad-flies occasionally lay their eggs upon the mucous membranes or surfaces of wounds, and from the eggs so laid larvæ may develop. The larva of an arachnoid (*Pentastoma denticulatum*) is alone found in the internal organs. In so far as these parasites penetrate into the tissues, they cause irritation and inflammation; the bite of insects that suck blood is also followed by an inflammation in the neighborhood of the puncture.

Attention has recently been directed to the possibility that mosquitos, stinging flies, gad-flies, bed-bugs, lice, etc., may be the **conveyers of an infection**, in that bacteria or protozoa may by chance be attached to their bodies, or that in the act of sucking blood of an infected man or animal they may take up into their bodies either bacteria or protozoa and later convey them to other individuals. So far as experience goes, the danger of such conveyal is not very great in the case of the majority of the infectious diseases, since the bacteria thus taken up die after a

time; yet it is probable that such conveyal does take place, as, for example, in plague, infection with pus-cocci, and anthrax. This method of conveyal is of chief importance in **malaria**, in that the *plasmodia* taken from the blood of infected individuals by mosquitoes (anopheles) *undergo further development in the body of the mosquito and produce a new generation, which through the bite of the mosquito is transferred to another individual*, so that the spread of malaria is accomplished through mosquitos. Similar conditions exist also in the case of the tsetse-fly disease and Texas fever of cattle, the latter being conveyed by ticks. Further, it is claimed by Manson, Sonsino, and others that the infection of man with the filaria is also brought about through the agency of mosquitos.

Of the parasitic protozoa there should be mentioned also the *Amœba dysenteriæ*. the cause of one form of dysentery in man; the *Trypanosoma evansi*, the cause of surra; *Tr. brucei*, the cause of the tsetse-fly disease or nagana; *Tr. gambiense* the etiological agent in human trypanosomiasis or sleeping-sickness; and the *Trichomonas* as a probable causal agent in catarrhal conditions of intestine or genito-urinary tract. Supposed protozoan parasites have also been described as the causal factors of small-pox, scarlatina, tick-fever in man, rabies, syphilis, tumors, etc., but convincing proofs are not yet at hand. A protozoal origin is also assumed by some writers for yellow-fever, partly because of the fact that the causal agent of this disease is conveyed by a mosquito, *Stegomyia fasciata* (*Reed* and *Carroll*).

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II. Congenital and Inheritable Anlage of Disease.

1. *Immunity, Predisposition, and Idiosyncrasy.*

§ 14. Toward the injurious agents capable of producing disease different individuals show very different powers of resistance, and such differences are exhibited particularly in the case of the infectious diseases and many poisons. When an individual is not susceptible to a given infection or poison, the property thus manifested is designated as *immunity* and as *insusceptibility to poison;* but if an individual is easily infected by a pathogenic microörganism, we assume that he possesses a *predisposition*

to the given disease. If influences of any kind having no effect on ordinary individuals are able to throw certain persons into a pathological condition, this phenomenon is explained through the assumption of an extraordinary sensitiveness, an *idiosyncrasy*.

Immunity and *predisposition* represent the opposite behaviors of an organism toward external injurious agents, but at the same time they cannot be sharply separated from each other. In very many cases the immunity is not absolute but only relative, so that the individual concerned may be made ill through a given harmful agent, for example, a pathogenic microörganism or a poison, when the agent acts in its characteristic manner and strength. On the other hand, the predisposition to a disease may be but slight, so that the latter occurs only under especial conditions.

An *absolute immunity* or *insusceptibility* is possessed by man against many of the microörganisms pathogenic for animals, for example, the bacteria of swine plague, swine erysipelas, and symptomatic anthrax, and this may rest upon the fact that the character of his tissue and tissue juices does not admit a localization and multiplication of the given bacteria, or that the poisons produced by the latter are not poisonous for man.

The human race is *very susceptible* to smallpox, vaccinia, measles, and influenza, so that the great majority of human individuals in the course of life acquire these diseases. In the case of other diseases, as scarlet fever, pneumonia, typhoid fever, diphtheria, the *susceptibility seems much less*, but it is not possible to determine exactly to what extent the greater rarity of these diseases is dependent upon the fact that the individuals not affected are not exposed to the infection.

In the case of many infectious diseases, there is a greater susceptibility shown in childhood than in old age; as, for example, diphtheria, whooping-cough, and scarlet fever. Further, there are also variations in the degree of susceptibility at different times, as, for example, an individual may be exposed at certain times to measles without becoming infected, while at other times under similar conditions he may contract the disease.

In the case of many pathogenic organisms there appears to be necessary for the entrance of infection a certain *favoring condition or temporary increase of susceptibility*. As evidence of this may be taken the fact that in the human alimentary canal, especially in the mouth and throat, as well as in the respiratory tract, pathogenic organisms (streptococci, staphylococci, pneumococci, tubercle bacilli) may be present without the occurrence of an infection. It may also happen that cholera spirilla may increase abundantly in the intestine without causing marked symptoms.

Such occurrences may be explained in part by a decrease or loss of virulence on the part of such bacteria, but this explanation cannot be applied to all cases. In many instances it must be assumed that the harmlessness of the bacteria is due to the ability of the tissues to hinder their entrance into the deeper parts. In some cases this may depend upon the structure and organization of the tissue, in other cases chemical substances may have a determining influence (see § 29). In favor of the first assumption lies the fact that tissue-lesions, which permit of the entrance of bacteria, bring about an infection. A *wound, therefore, in whatever way produced, forms a local predisposition*, and the disease, in such cases, bears the character of a **wound-infection.** Infections caused by pus-cocci, tubercle bacilli, tetanus bacilli, glanders, and anthrax bacilli are often of this character.

Other causes leading to an increased predisposition to infection are less easily recognized. It appears that severe *chilling*, "*taking of cold*," or *hunger* may have this effect; also *changes in the tissues due to preceding infectious or non-infectious local or general diseases* (see § 11, Secondary Infections). In the case of intestinal infections (typhoid, cholera), *gastro-intestinal disturbances*, diminished acidity of the stomach contents, overloading of the intestines, retention of the contents, etc., play an important rôle. Not infrequently it is impossible to determine what causes have favored the production of an infection at a given time.

Special predisposition or special **lessened resistance of the organism** is also not infrequently shown to other injurious agents than those of infectious nature. Certain individuals are less able than others to stand external high temperatures, particularly if at the same time bodily labor is performed. Of the soldiers on a march only a fraction may suffer from heat-stroke, although all are under the same conditions. The altitude at which different individuals, during mountain ascents and balloon voyages, become sensible of the deficiency of oxygen, varies greatly. The effects of chloroform anæsthesia differ greatly in different individuals. Many persons become exhausted through physical or mental labor at a time when in other individuals, under like conditions, no trace of such exhaustion is discoverable; and such influences operating daily upon a brain, in cases of especial predisposition, may lead to diseased conditions.

Occasionally certain individuals show a sensitiveness toward particular external influences, which is wholly anomalous to that usually observed, so that symptoms of disease may be caused by influences which ordinarily do not affect the majority of mankind. Such a peculiar sensitiveness is designated **idiosyncrasy**. It is exhibited particularly in reference to certain chemical substances, in that certain articles of food or drink regarded as harmless act upon such persons as poisons. The eating of fresh fruit or sugar or salad produces, in certain individuals, nausea and vomiting. Others have an aversion to partaking of dishes prepared from liver or kidneys, and become ill if they overcome this aversion and eat these foods. Others still, after eating crawfish, lobster, strawberries, raspberries, morels, or asparagus, are affected with urticaria, a disease characterized by an eruption of itching wheals, colic, and vomiting. Not a few persons are unable to drink boiled milk without unpleasant results therefrom. Alcohol, even in very small doses, may in certain individuals cause marked excitation, or narcosis, or remarkable disturbances of the vaso-motor system. The drinking of cocoa may cause cardialgia and dyspeptic symptoms. Doses of morphine or chloroform, which are borne by the majority of mankind without injury, may cause in certain individuals severe symptoms or even death. Some individuals show a high degree of sensitiveness, on the part of the mucous membranes of the respiratory tract, to the pollen of certain grasses, so that during the time of the hay-harvest the inhalation of the pollen which is widespread through the air gives rise to a catarrhal condition of the nose and conjunctiva, often of the larynx, trachea, and bronchi, which in severe cases may be associated with asthma and fever. These conditions are known as *hay-fever*, *hay-asthma*, or as pollen-diseases. According to the investigations of Dunbar, the pollen contains a substance that may be extracted, and, when injected subcutaneously into those disposed to this disease, causes the characteristic symptoms of intoxication. Disinfecting fluids, corrosive sublimate or carbolic acid, in solutions

which are ordinarily borne without discomfort, may, when applied to the skin of certain individuals, cause not only local disturbances of sensation and inflammation, but under certain conditions may excite an eczema that spreads over a large part of the body.

On what the peculiar idiosyncrasy in individual cases depends is not clear. In many cases an especial excitability of the nervous system or of certain parts of the same may be regarded as the cause of the phenomenon. In the case of an idiosyncrasy toward chemically active substances, it may be assumed that the affected cell-protoplasm contains atomic groups which combine with the given substance.

The great importance of the part played by natural predisposition and immunity in the origin of infectious diseases has not only been made evident by the study of the spread of epidemics among men and animals, but has received also abundant confirmation by numerous experimental investigations. If, for example, a mixture of different bacteria be injected into an animal, only a part of these will develop and produce tissue-changes; the others die. If the same mixture be injected into an animal of a different species, the bacteria which develop are not the same as those in the first case. Further, a certain form of bacteria, which when inoculated into a certain species of mouse invariably causes death, may, when inoculated into another mouse of different species, be without effect. Mice are very susceptible to anthrax, rats are nearly immune. The poison of the so-called septicæmia of rabbits kills with absolute certainty rabbits and mice; guinea-pigs and rats are immune to it, while sparrows and pigeons are susceptible. The spirilla of relapsing fever may be successfully inoculated only into apes. Gonorrhœa, syphilis, and leprosy cannot be successfully inoculated into any of the lower animals with the exception of apes.

In the case of a *natural antitoxic immunity* the toxins that may enter the organism may remain as perfectly harmless material in the body, and only relatively late are split up in the process of metabolism. In such cases the avidity between the toxin and the body cells, their receptors respectively, may be entirely wanting or very slight. When not entirely wanting, an increase of the dose may produce intoxication. An immunity against small doses may arise through the anchoring of the poison (for example, tetanus poison) to tissue elements whose changes do not produce symptoms of disease; or antitoxins may be present which render the toxins inert.

The *especial diseases* to which the *new-born* so frequently succumb are, aside from the conditions acquired during intra-uterine life, dependent partly upon a pathological weakness of the entire organism (especially in case of premature birth), and partly upon the surrounding conditions. Asphyxia, which is of such frequent occurrence, may arise either as the result of bodily weakness or of pathological influences exerted during delivery. Infectious diseases may be acquired through the stump of the cord or through the accessible mucous membranes and respiratory tract during birth. Hæmorrhages are dependent partly upon traumatic influences exerted during birth, partly upon disturbances of circulation and upon infections.

Nurslings and also older children are *more susceptible to many infections* than adults; particularly so in the case of whooping-cough, diphtheria, measles, scarlet fever, and tuberculosis. In the intestine of nursing infants, bacilli, tubercle bacilli in particular, are very easily taken up into the lymph-vessels; the skin of infants also offers less resistance to the entrance of pus-cocci than that of older individuals. Young dogs may be easily infected with anthrax while old ones cannot. In this connection it should be noted that the slight susceptibility or the immunity of many adults is dependent upon the fact that they owe their immunity to attacks of such diseases during childhood. Further, it should be remarked that children are more exposed to certain infections, for instance, tuberculosis, than are adults.

In *later life* hæmorrhages, softening of the brain, cardiac degenerations, cancerous growths, and the formation of gall-stones are of especially frequent occurrence. The disease of the arteries known as arteriosclerosis, and also gout, may appear even in the late years of middle life. The *predisposition in old age to certain diseases* depends in part upon degenerative processes, associated with premature senility of the tissues: in part also upon the fact that certain infl ences, which the years bring with them, gradually accumulate, so that finally the changes which they produce become so prominent that they lead to functional disturbances, and thereby to recognizable morbid conditions. Moreover, it is to be remarked that many pathological symptoms of old age are secondary diseases, which become apparent only after other tissue-changes have reached a certain degree. For example, senile hæmorrhages, senile gangrene, degenerations of the brain and heart are dependent upon disease-processes occurring in the arteries.

The *predisposition of the sexes* to certain diseases depends, in the first place, upon the especial structure and function of the sexual apparatus. The conditions of pregnancy and the puerperium offer an especially favorable field for many diseases, as, for example, for infection through wounds. Moreover, different relations of the sexes to many diseases may be explained by differences in the modes of labor and in the habits of living of the two sexes.

Differences of predisposition of different races are shown particularly in regard to malaria and dysentery, toward which the negro in general shows less susceptibility than the European. Malarial parasites may be present in the blood of the former without giving rise to symptoms of disease.

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2. *Inheritable Diseases Arising from Congenital Pathological Anlage.*

§ 15. Among the **morbid conditions arising from congenital anlage**, and which either appear spontaneously or are developed through any external influence whatsoever, there may be distinguished different groups; namely, one in which the body as a whole—the constitution—is involved; another in which only a part of the body as a system or an organ is affected; and, finally, a third in which only a part of an organ presents functional or anatomical changes of a pathological nature. It must be noted that there is no sharp dividing line between these groups, inasmuch as local pathological changes may be associated with constitutional conditions. Further, it is often very difficult or impossible to determine exactly what part the *anlage* and what part extrinsic causes have

taken in the production of such pathological conditions, inasmuch as the force of the external influence which has called the pathological process into activity cannot be estimated with certainty.

Among the **constitutional diseases arising from intrinsic causes** are to be mentioned, first, the **development of dwarfs** and **giants,** disturbances of growth, the first of which is marked by an under-development of all the parts of the body, both of the skeleton and the soft parts, while the second is characterized by a growth exceeding that of the ordinary individual. It cannot be doubted that both dwarf and giant growths are often purely dependent upon a congenital anlage; but the same effects can be produced, at least in so far as the inhibition of growth is concerned, by harmful influences exerted during the period of development and growth. It cannot always be told with certainty whether an abnormal bodily growth is dependent upon a congenital anlage or upon pathological influences during the period of growth, as, for example, defective development or disease of the thyroid gland.

The same difficulty is presented in cases in which the body has attained full development of stature, but manifests a **general feebleness of constitution,** as shown by its inability to withstand a great variety of external influences. Such condition may arise either from congenital defective and weak anlage or from harmful influences which have attacked the developing body during intra- or extra-uterine life; or further, congenital weak anlage and external weakening influences may have affected the development of the individual in an equal measure.

A further constitutional peculiarity, which is founded upon a special congenital anlage, is **corpulence** (*obesity, adipositas, lipomatosis universalis*), a condition in which fat is deposited in an excessive amount, either in the tissues normally containing fat, or further, in regions which normally contain no fat, as, for example, beneath the endocardium or between the muscles. The increased deposit of fat is ultimately to be referred to a disproportion between fat-production or fat-supply and fat-consumption, the pathological increase of fat being at one time dependent upon an abnormal increase of fat-production, at another on a decrease of fat-consumption. Daily experience teaches that the energy with which metabolism goes on in the body differs greatly, and changes also at the different periods of life, so that the normal amount of nourishment tends at one time to fatten, at another time does not.

In the pathological condition termed obesity, which in part rests upon a congenital tendency, the energy of the protoplasmic forces of destructive metamorphosis is weakened, so that an abnormal amount of fat is deposited, even when only a moderate or even a decreased amount of nutritive material is supplied to the tissue.

Gout, like obesity, is also a constitutional disease, which is chiefly dependent upon a congenital anlage and is produced essentially by intrinsic causes. The exact nature of the disease is not yet known. It is characterized by deposits of uric acid in the tissues. According to Garrod and Ebstein, the acute attacks of gout are caused by an accumulation of uric acid which has its origin either in the kidneys or in local conditions. On the other hand Pfeiffer holds that the essential feature of the gouty tendency consists in the fact that the uric acid is produced in a form which is soluble only with difficulty. According to von

Noorden, the formation and deposit of uric acid is only a secondary process, which is induced by the presence of a certain ferment having only a local action, and is consequently not dependent upon the amount or character of the uric acid formed in other parts of the body.

Pathological changes arising in single systems and organs from congenital anlage may occur in any part of the body, and may involve an entire system or organ, or only a part of one.

In the **skeleton** there may occur abnormal development of single parts, as, for example, an abnormal smallness of the extremities (micromelia) or of the head (microcephalus) in contrast to the size of the trunk; an abnormal over-development of a bone or group of bones (macrocephalus, macrodactylism, giant growth of a finger, entire foot, or of an extremity); malformations of the extremities (cleft-hand, cleft-foot, etc.). Occasionally supernumerary bones, as carpal bones or phalanges, may develop, giving rise to supernumerary fingers. Further, there may be developed atypical formations, such as bony outgrowths (exostoses, hyperostoses), which may extend over the skeleton to a greater or less extent, originating either spontaneously or following some traumatism.

In the **muscular system** there occur particularly pathological bony formations, either single or multiple (myositis ossificans), which, in the period of childhood, occasionally lead to a progressive stiffness of the muscles, through the transformation of muscle into bony plates.

In the **vascular system** there occur either gross anatomical changes, such as abnormal branching of the arteries, pathological development of the heart, or finer changes, which reveal themselves through some abnormal action on the part of the circulatory apparatus or through a tendency to hæmorrhages (*hæmophilia*) which take place spontaneously, that is, without our being able to demonstrate the action of some injurious influence upon the heart or blood-vessels.

During the development of the **central nervous system** there may occur primary disturbances, which in part may manifest themselves only through some *pathological disturbance of function* or *some special predisposition to disease*, while others are distinguished by *gross anatomical changes*, such as abnormal smallness of the brain (micrencephalon) or of the spinal cord (micromyelia), defective development or absence of particular parts (see chapter on malformations), misplacement of the gray matter (heterotopia of the gray substance), abnormal formation of cavities (syringomyelia), or abnormal formations of neuroglia. These disturbances may involve the functions of the sensory organs and the motor centres, and even to a greater extent the psychical processes. The morbid conditions known as idiocy, epilepsy, periodic and circular insanity, hysteria, neurasthenia, as well as paralysis, mania, melancholia, and dementia, may have their origin in a congenital predisposition. Recently the tendency to crime has also been ascribed to a congenital predisposition, and Lombroso, in particular, has endeavored to prove that the man who lives only through crime and for crime, the *Homo delinquens*, is a congenital criminal—that is, a man who suffers from bodily and mental abnormalities, who possesses other physical and psychical characters than the normal man or even than one who is simply mentally unbalanced, in that he presents the symptoms of a form of degeneration tending in a well-defined direction. According to Lombroso, a subnormal development of the anterior half of the cranium, associated with a corresponding lack of development of the anterior portion of the

cerebrum, in connection with an over-development of the posterior portion, produces a feebler development of the intelligence and of the moral sense, and favors a strongly developed instinct-life. Benedikt even goes so far as to maintain that the criminal possesses a peculiar configuration of the cerebral convolutions, similar in type to those of beasts of prey.

The views of Lombroso and Benedikt have met with much opposition, and have been attacked as incorrect. There can be no doubt that there does not exist a degenerate species of the human race, which is characterized by such anatomical peculiarities as to make it possible for us to distinguish a class of *Homo delinquens* from that of *Homo sapiens*. All the somatic peculiarities regarded as characteristic of the criminal type—as, for example, the beast-of-prey type of cerebral convolutions, slightly developed frontal brain, receding forehead, massiveness of the lower jaw, prognathia, asymmetry of the cranium, marked prominence of the arcus superficialis and arcus frontalis, pathological conformations of the skull, etc.—while relatively frequent in criminals, are also far from being infrequent in normal men. On the other hand, it is not to be doubted that the tendency to crime is very frequently dependent upon a congenital predisposition having its seat in some special organization of the central nervous system. In this respect the criminal resembles the insane individual; further, mental diseases—for example, epilepsy and hysteria—are often observed in criminals.

Pathological cerebral functions may develop primarily in individuals possessing such morbid predispositions—that is, without external influences playing any part in the production of the disturbance, so that the person concerned may manifest pathological disturbances of cerebral functions without the concurrence of any external injury, either during the period of development and growth or later. On the other hand, in other cases, external influences—such as mental work, sorrow, care, psychical irritation, disease, etc.—are the causes which give rise to the particular illness—that is, to the occurrence of pathological brain or spinal-cord functions. In these cases the inherited tendency consists only in an abnormal weakness, a predisposition to disease of the central nervous system, so that insignificant influences which would produce no recognizable effects upon a normal individual are sufficient to excite the morbid phenomena. Since many influences, as diseases, infections, psychical irritations, are adequate under certain conditions to produce mental diseases in individuals who must be regarded as normal, it is clear that in many instances it is difficult and often impossible to determine what part the intrinsic causes—the inherited predisposition—and what part the extrinsic causes have had in the production of a disease of the central nervous system.

In the case of the **peripheral nerves**, it is especially their connective-tissue elements which often take on a pathological activity of growth under the influence of intrinsic causes. This activity may manifest itself partly in the form of diffuse thickenings (fibromatosis of the nerves), which are situated either along the course of those nerves large enough to be dissected with the knife or along the finer nerves, often in large numbers through the entire nervous system, and occasionally involving the entire territory of the peripheral nerves, the skin being most frequently affected (multiple fibromata of the skin). In individual cases the fibromatosis of the nerves is associated with an increase in the number of nerve-fibres, so that within a given area of nerve-distribution there will be found a great increase of nerve-fibres, thickened through a

pathological increase of the endoneurium and for the greater part twisted and wound into serpentine forms (cirsoid neuroma, plexiform neuroma).

Among the **congenital pathological conditions of the visual apparatus** are to be mentioned in particular dyschromatopsia and achromatopsia, congenital partial or total color-blindness, which are frequently spoken of as Daltonism, and are characterized by a want of perception for certain colors (most frequently for red and green) or for all the colors. In this same category belongs further the typical pigment degeneration of the retina, in which there occurs a peculiar spotted, black pigmentation of the retina, associated with a diminution of central sharpness of vision and light-perception, with a narrowing of the visual field. Finally, certain forms of myopia, also albinism (absence of pigment in the choroid), the latter condition also involving the structures of the skin, are to be considered in this connection.

Of intrinsic conditions of the **auditory apparatus** deaf-mutism is of chief importance; this condition, in part at least, is dependent upon a primary disturbance of development. Further, certain malformations of the external ear fall into this class.

In the **skin** and **subcutaneous connective tissue** new-growths may develop from congenital anlage, consisting of proliferations, sometimes of connective tissue, at other times of epithelium. They often involve particular parts of the skin, as the cutaneous nerves, blood-vessels, lymph-vessels, or the adipose tissue. When occurring as extensive thickenings of the skin and subcutaneous tissue, they constitute the foundations of the conditions known as fibromatous, neuromatous, hæmangiomatous, lymphangiomatous, and lipomatous elephantiasis. As circumscribed growths they are known as birth-marks, fleshy moles, lentigines, freckles, and tumors of the blood- and lymph-vessels. The epithelial hypertrophies give rise to those conditions designated as fish-scale disease or ichthyosis, ichthyotic warts, and cutaneous horns.

In addition to the pathological conditions which have been mentioned, there are also **malformations of the body** (see chapter on malformations) **or also of internal organs** which must be regarded as primary—i.e., which are not produced by injurious influences exerted upon the developing fœtus. Finally, many forms of **tumors** (see chapter on tumors) are to be placed in this class, particularly those which are found to be already developed at birth or which develop during childhood.

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See also § 17.

§ 16. **The origin of congenital pathological anlage**—that is, of diseases in which extrinsic influences are either entirely absent during both intra- and extra-uterine life, or are of significance only as a source of irritation sufficient to excite into development pathological tendencies already present in the body—may be explained in two ways: *Either the pathological peculiarities of the individual concerned are inherited from the ancestors, or they are developed from the seed,* i.e., *from the individual sexual nuclei that have copulated or from the segmentation nucleus resulting from their union.*

The inheritance of pathological qualities is a fact clearly shown by clinical observations, inasmuch as many of the examples of diseases due to intrinsic causes which are cited in § 15 also appear as inheritable characteristics in certain families. In some cases these characteristics are transmitted from the parents to the children, in other cases the grandchild may exhibit pathological peculiarities of the grandparents, the parents themselves remaining exempt; finally, in other cases the pathological peculiarity may be manifested in individuals of the collateral branches, as from uncle to nephew. Dwarfishness and giantism are pathological peculiarities which frequently characterize certain families. Six fingers, cleft-hand and cleft-foot, hare-lip, dextrocardia, birth-marks, multiple exostoses, fibromatosis of the nerves, and multiple neurofibromata may appear in families for many successive generations.

Congenital hæmophilia is also an inheritable condition, which is ordinarily transmitted through the daughter to a male grandchild, the daughter not showing the disease. There may occur, however, a direct transmission of hæmophilia from parents to children. Partial or total color-blindness also occurs as an inheritable family disease, especially affecting the male members, and like hæmophilia is transmitted through the female line, which does not suffer, to the male descendants. The typical pigment-degeneration of the retina, myopia, deaf-mutism, certain forms of progressive muscular atrophy, and polyuria (Weyl) are also inheritable.

According to Gairdner and Garrod, in about ninety per cent of the cases of gout there is a family history of the disease.

Of the pathological conditions of the nervous system many are inheritable; to these belong especially periodic and circular insanity, epilepsy, hysteria, congenital insanity, and to a somewhat less extent

melancholia, mania, delusional insanity, and alcoholism. Progressive paralysis, the deliriums, and the conditions of nervous exhaustion are but slightly influenced by heredity (Kraepelin). Hagen estimates the number of hereditary insane at 28.9 per cent, Leidesdorf at 25 per cent, Tigges at over 40 per cent of all cases, while Forel holds that 69–85 per cent have hereditary taint.

In the most severe forms of hereditary degeneration the pathological condition itself is inherited, but more frequently the predisposition to disease is alone inherited and the morbid condition itself is developed through the action of extrinsic harmful influences upon the central nervous system. The character of the disease in the descendants may be the same as in the ancestors (*identical heredity*). More often the character of the disease is changed (*transformational heredity*), not infrequently in the sense that the severity of the condition increases from generation to generation (*degenerative heredity*).

According to Morel, there may appear, for example, in the first generation, nervous temperament, moral depravity, excesses; in the second, a tendency to apoplexy, severe neuroses, alcoholism; in the third, psychical disturbances, suicidal tendency, intellectual incapacity; finally, in the fourth, congenital idiocy, malformations, and arrests of development.

The occurrence of **inheritable diseases** is by no means remarkable; it is a well-known fact that in a family not only the peculiarities of race, but also of that particular family are inherited, and that very often the characteristic qualities of either parent or of both recur in the children. As a hypothesis for the explanation of heredity, it is only necessary to assume that the peculiar quality under consideration represents not merely a somatic change accidentally acquired during the life of the ancestor, but much rather a quality of the ancestor developed from a **congenital anlage.** Diseases which in a normal individual arise only under the influences of some external injurious influence are never in a true sense inherited (compare § 17), but only those *pathological conditions existing in the germ* are to be regarded as examples of true inheritance. If a certain disease, as, for example, a mental disease or myopia, is the product of a special inherited predisposition plus the effect of injurious influences which have acted upon the body during life, only that part can be transmitted which has its seat in some peculiar congenital anlage, but not that caused by external influences—the acquired condition cannot be inherited.

In *direct inheritance*—i.e., in that form of inheritance in which parental qualities are transmitted to the child—the transmission of normal as well as of pathological qualities is possible only when both sexual cells, in the condition in which they combine, contain the potentialities of the characteristics of both parents, in so far as these characteristics are transmissible. The product of the union of the sexual cells—the segmentation-cell—must, therefore, contain within itself both the paternal and maternal qualities. Since the sexual cells do not represent a product of the body developing during the course of life, but are rather to be regarded as independent structures, which at an early period of development are separated from the other parts of the body (that is, from the somatic cells) into special organs, where, protected and nourished by the body to which they belong, they lead an independent existence; the only possible explanation for the phenomenon of inheritance is found in the hypothesis that the individual sexual cells contain, from the time of their origin onward, the potentialities of the same qualities which appear

in the body in which they dwell. Both the sexual cells and the body itself, therefore, inherit in general the same qualities from the ancestors. Since in the act of fructification only the nuclei of the sexual cells—that is, parts of the same—come to copulation, we are compelled further to assume that the nuclei are the bearers of inheritable qualities, and the peculiarities of the individual arising from the combination of the sexual nuclei have their foundation in the organization of the nuclei.

The appearance in the descendants of normal or pathological characters belonging to the collateral relatives (uncle, great-aunt, or cousin), but which are not present in the parents, is known as *collateral inheritance*. This phenomenon is explained by the hypothesis that the sexual cells, in their origin, received characteristics which the bodies of the parents did not receive, or which, at least, did not undergo development and manifest themselves in the parental bodies, whereas in certain relatives they did become manifest.

The appearance in an individual of normal or pathological characteristics which were wanting in the parents, but were present in the grandparents or great-grandparents, is known as *atavistic inheritance*. This phenomenon is explained by the hypothesis that given characteristics of the grandparents or great-grandparents were transmitted to the sexual cells of the son, or of the son and grandson, without developing in the body of the first, while the quality thus remaining latent became again manifest in the grandson or great-grandson.

The attempt has been made to give to the atavistic mode of transmission—which is of frequent occurrence and is usually confined to the immediate generations of ancestors—a wider significance in pathology. Thus it has been proposed to explain the occurrence of many newly arising pathological conditions, which appear similar to certain somatic qualities possessed by remote animal species in the ancestry of man, as a reversion to the type of these ancestors. For example, microcephalus and micrencephalus have been explained as a reversion to the ape type; and Lombroso is inclined to regard the *homo delinquens* as an atavistic phenomenon. There can be no doubt that certain writers have gone too far in this respect and have mistaken certain acquired pathological formations or new germ-variations (compare § 17) for atavistic conditions. Aside from the question of reversion to the type of the nearest generations of ancestors, atavism plays but an insignificant part in pathology, and it can really be employed only in the explanation of pathological formations in which the tissues show a certain fluctuation of behavior, so that not rarely formations arise which in phylogeny or ontogeny represent stages of the then normal conditions. In this category belong, for example, the occurrence of certain forms of the ear, supernumerary ribs, nipples, or mammary glands, and the development of certain muscles which are found in the most closely related mammals.

It is held by many writers that *in individual cases, acquired pathological conditions may, under certain circumstances*, be transmitted *to the descendants*. Some even affirm the possibility of hereditary transmission of deformities caused by injury, and regard such transmission as proved in certain cases. In support of their view they believe that they can refer to the hereditary transmission of birth-marks, malformations of the fingers, myopia, mental diseases, predisposition to tuberculosis, etc., as examples, according to their assumption, of diseases which appeared in the first instance as acquired, and which were then transmitted to the descendants. Further, they hold that they can point to observations on animals, of which numerous accounts are found in the literature, as giving evidence that injuries may cause deformities which are later transmitted to the offspring.

An unprejudiced examination, however, of the material collected in support of this view shows that *observations which establish the hereditary transmission of pathological characteristics acquired in the individual do not exist.* The alleged proofs are found in part to be based upon inaccurate observations, in part upon incorrect inferences drawn from accurate observations. For example, the assumption that the occurrence of a birth-mark in a child in the same region of the skin as that in which the mother has a scar is a proof of inherited deformity is wholly in the wrong, inasmuch as birth-marks and scars represent two entirely different pathological processes. If, among the descendants of a man who suffered from some form of mental disease and who showed this disease only after a certain age through the perversity of his actions, there appears an inheritable disease of the central nervous system, or if we note a similar occurrence in the case of myopia, we cannot conclude from such observations that the disease of the ancestor was purely an acquired condition. The term *acquired*, in the biological sense, can be applied only to that which in the course of the life of an individual arises purely from extrinsic influences, but not to a quality, the anlage of which existed already in the germ-cell, although this quality did not become manifest until excited to development by extrinsic influences. Should there appear in a family inheritable mental diseases or hereditary myopia, the first case of such diseases may have already been due to some pathological alteration of the germ, although no manifestations of the disease occurred until some of the outside influences of life excited it to activity, and so rendered possible the recognition of the pathological condition. The particular pathological condition in this case cannot, therefore, be regarded as a purely acquired disease.

The observations of *Brown-Séquard* that guinea-pigs, in which epilepsy has been experimentally induced, can transmit the condition of epilepsy, have been shown by *Sommer* to be incorrect, in that the condition is not a true epilepsy, but a reflex epilepsy, and is not transmitted.

Against the occurrence of an inheritance of acquired pathological conditions is the simple consideration that the human race, which is exposed to so many injurious influences, and whose individual members suffer so frequently from disease and mutilations, would very soon arrive at a state of extreme misery and stunted growth and would eventually perish were only a small part of the acquired diseases transmitted to the descendants. Further, the origin of man and animal forms reproducing through germinal cells is in itself an argument against the possibility of the transmission of qualities acquired by the individual.

The act of fructification—that is, the first step leading to the production of a new individual—is accomplished by the copulation of the sexual nuclei—that is, of the nuclei of the ovum and spermatozoön. According to the researches of the last decades, there can be no doubt that *these nuclei are the bearers of the hereditary characteristics of the parents*, and that the individuality of the copulating nuclei is inherent in the organization of the same. It is impossible to conceive in what manner processes taking place in the body cells can produce in the sexual nuclei, which lie within special cells in the sexual glands, such alterations of organization that they shall contain in potential form the acquired characteristics of the body and transmit them, after copulation has occurred, to the descendants.

Delage was able to fructify non-nucleated portions of the eggs of echinoderms, annelides, and mollusks with spermatozoa (merogony). He regards the union of the nucleus of the spermatozoön with the protoplasm of the egg as the essential feature of fructification. This is not applicable to the ordinary method of fructification, but only shows that in exceptional cases the entrance of the spermatozoön into the protoplasm of the egg is sufficient for the setting-up of further development, and that the nucleus of the spermatozoön entering into the egg without uniting with the nucleus of the latter exercises an especial influence upon the protoplasm of the egg.

Darwin in his time represented the view that acquired characteristics could be transmitted to the descendants, and endeavored to make such phenomena intelligible by the theory that molecules from all the cells of the body contribute to the formation of the germ-cells, and that, consequently, alterations of the organism can be transmitted to the germ-cell. Nevertheless, there occur in the writings of *Darwin* statements which not only do not agree with this opinion, but directly contradict it.

At the present time the views with regard to the inheritance of disease generally accepted are that there is no true inheritance of infections and that gross structural disturbances cannot be inherited. The only possible inheritance of conditions acquired by the parents is that of conditions acting both upon the somatic tissues and germ-cells of the parents. Chemical and physical conditions acting within the body or from without may cause changes in the constitution of somatic and germ-cells. The occurrence of such changes in the germ-cells is clearly shown in the effects upon the progeny of paternal or maternal alcoholism, plumbism, and experimentally with abrin. It is a

well-known fact that in the case of the birth of monsters there is often obtainable a history of some infection in one of the parents before conception took place. Bardeen's experiments regarding the changes in embryos arising from ova fertilized by spermatozoa that had been injured by Roentgen irradiation are very suggestive.

Adami has applied the side-chain theory in explanation of heredity. According to this view there may be also a true inheritance of morbid conditions due to modifications in the biophoric molecules through the interaction of their side-chains.

Recently much discussion has been waged over the principles of heredity involved in *Mendel's law*, *Galton's law*, and De Vries' *theory of mutations* (see literature).

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See also § 15 and § 17.

§ 17. As has been explained in § 17, *inherited diseases are always such as have at the very first developed from intrinsic causes, that is, from certain anlage in the germ-cells;* or *at least are diseases in which the predisposition thereto is a congenital characteristic.* Conversely, the statement may be made *that all normal or pathological qualities in the germ-cells are inheritable.*

The **first appearance of new pathological characteristics which are inheritable** may be dependent upon the fact that as a result of **sexual procreation**—i.e., of the union of two sexual nuclei, one of which is the bearer of the transmissible qualities of the father, the other of those of the mother—**new variations** are constantly arising, so that the child is never exactly like one parent; but, on the other hand, in addition to the qualities which the parents offer, it possesses also new qualities. Even if we assume that the sexual nuclei at times contain in potential form exactly the same characteristics as those of the parents, the product resulting from the copulation of these nuclei would present a certain degree of variation. In such a case, however, the differences between the children of such parents would be but slight. As a matter of fact, the different products of the same parents may show an infinite variety, by reason of the fact that the germ-cells themselves contain further a mixture of the transmissible characteristics of the paternal and maternal ancestors, and that this mixture is never the same in the individual germ-cells.

In accordance with this is the fact that the children of a certain family always present important differences in both physical and mental qualities. A marked resemblance occurs only in the case of twins arising from one egg—i.e., when the process of development of both children has started from the same act of copulation.

The **embryonal variations resulting from the mixture of two individually different hereditary tendencies** can find their expression in the most varied qualities of the body and mind of the developing child. If these do not deviate in a marked degree from the characteristics which the different members of the family show, the conditions are regarded as normal and ordinarily receive no especial attention. If, on the contrary, important differences of character are produced, the occurrence attracts greater attention; and, according to the value which it has for the individual concerned, is regarded at one time as something favorable, at another time as something unfavorable, something pathological. When small, weak parents produce children who develop into large and strong individuals, or when the intellectual capacity of the children surpasses that of the parents, the occurrence is regarded as favorable. If, as actually happens, a genius in any branch of human knowledge or skill suddenly appears within a family, without any evidence of an especially marked mental development in the ancestors, the phenomenon would attract general attention and be regarded as a fortunate event. But if, on the other hand, strong parents beget children who are weak or physically defective, or if they show a mental development inferior to that of their parents, or if they show a complete stunting of a part of their mental faculties, *the newly appearing variation is regarded as abnormal, pathological.*

If we consider the experiences which the pathology of man and animals furnishes, the assumption seems fully warranted that of the **transmissible pathological conditions and predispositions**, very many, perhaps the majority, **are referable to a variation of the germ based upon the amphimixis.** For example, the group of hereditary pathological conditions and predispositions of the central nervous system, hereditary myopia, hæmophilia, pigmentation of the retina, and polydactylism may arise in this manner. If such abnormal characteristics show themselves repeatedly in the children of the parents, who are themselves normal and have healthy ancestors, it may be assumed that the germ-cells of the parents, though individually normal, have through their union given rise to a pathological variation. This hypothesis becomes substantiated when one or both parents produce normal offspring through copulation with other individuals.

Besides the variations which are the result of normal sexual reproduction, it is very probable that pathological germ-variations which lead to the development of transmissible pathological qualities may also arise through the action of **injurious influences upon the sexual nuclei or the segmentation nucleus**; or else that the **process of copulation**—that is, the union of the sexual nuclei—**has been disturbed** in some manner. The injurious substance may be a body-product, or it may come from without, and at the same time also produce its harmful effects upon the body. Consequently, in these cases we may speak of the **germinal acquisition** *of a transmissible pathological characteristic through the action of an extrinsic injurious influence.* This does not mean, however, as has been accepted by many, that the tissues of the body, under the influence of extrinsic harmful influences, first suffer changes in themselves, and then transfer these changes to the germ-cells. It is to be believed, rather, that the harmful influence acts directly upon the sexual nuclei or the segmentation-nucleus, producing in these a *change of some kind,* which later leads to a pathological development of the individual developing from the impregnated egg. It is a matter of no importance, so far as the nature of the resulting pathological variation is concerned, whether the somatic tissues also suffer changes, or of what nature such changes may be.

If a transmissible pathological characteristic arises, it may, in case it does not affect life or prevent reproduction, actually be transmitted, although this does not necessarily follow. The chances that a particular characteristic will be transmitted are greatest when both parents possess the same quality, as, for example, when both parents are affected with hereditary deaf-mutism or with near-sightedness. If the characteristic is wanting in one parent, there is produced most frequently a new germ-variation, in which the pathological characteristic fails entirely to manifest itself, and in the following generations may completely disappear. If several descendants are begotten, the pathological characteristic, in case it is not wholly lost, may show itself in only a few of the descendants, and in these in either a modified or in an aggravated form. Not rarely it happens that the characteristic remains latent in one generation—that is, is confined to the sexual cells, and appears again in the second generation.

There seems to me to be no doubt that, through the copulation of two sexual nuclei possessing different hereditary tendencies, variations may be produced, and that among these there may be some which are to be regarded as pathological. It is more difficult to answer the question whether, besides these, there are not also transmissible variations of a pathological nature, which arise through influences which affect the

nuclei of the ova or of the spermatogonia, the spermatocytes or spermatosomes, or the segmentation-nucleus; and further, if we accept the existence of such variations, with what frequency do they occur. *Weismann* holds the opinion that the basis of transmissible variations is to be found, not in the amphimixis, but rather in the direct action of external influences upon the sexual nuclei. Starting from the assumption that the variable cells or cell-groups derived from the germ (by him designated as *hereditary pieces* or *determinates*) are represented in the germ-plasma by special particles, which are formed by the grouping together of a number of *life-trophoblasts* or *biophores* (molecular groups which represent the smallest units of life), and which he calls *determinants* or *determining pieces*, he believes that he is warranted in ascribing the transmissible variation primarily to the changes produced by external influences in the determinants or group of determinants contained within the nuclear chromatin, so that finally the hereditary pieces or determinates derived from them also suffer changes. He believes that such an influence might be exerted by excessive nourishment of a determinant, causing it to grow more rapidly. For example, he regards it as possible that many congenital malformations (for example, an increase in the number of fingers and toes) can be referred to a reduplication of the determinant-groups caused by increased supply of nourishment. According to *Weismann*, the amphimixis has only a secondary influence in the origin of a permanent variation, in that it mixes in constantly new manner the variations dependent upon the changes in the determinants, but does not in itself produce *new* variations. "The deviations which the determinants suffer through unequal conditions of nutrition constitute the material out of which, through amphimixis in connection with selection, the visible individual variations are produced, through whose increase and combination new forms arise."

I agree with Weismann in so far as the assumption that the appearance of a new variation of pathological nature is *in part* to be referred to changes in the determinants contained within the sexual nuclei, due to the direct action of extrinsic influences. I do not, however, believe that there is sufficient ground for attributing, as does Weismann, the formation of new separate parts to an over-nourishment of single groups of determinants. Such a dependence of the germ-plasma upon the surrounding nutritive material seems to me scarcely conceivable, and is opposed to all views hitherto held regarding the nutrition of cells. Not only quantitative but much rather qualitative changes of the food-material would appear to be necessary in order to produce changes in the organization of the determinants. Further, I hold that the amphimixis has not only a secondary but much more a primary significance with regard to the origin of pathological variations, in the sense that it itself is able to produce new variations. Finally, it seems to me that we cannot at the present wholly set aside the hypothesis of *Nägeli*, according to which the idioplasm is capable of altering its own condition, from within outward, in certain fixed directions and according to certain fixed laws, and thus may produce new characteristics.

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See also §§ 15 and 16.

§ 18. Besides the inheritable pathological conditions mentioned above, there appears to be a **hereditary transmission in the case of the infectious diseases**; but this is in reality not a **true form of inheritance**, and is more properly designated as **postconceptional intra-uterine infection.**

If pathogenic micro-organisms enter into the blood-stream of a pregnant woman they may be carried into the vessels of the maternal placenta, and finally may pass through the fœtal placenta into the body of the fœtus. Such a transmission has been positively demonstrated in many infections (staphylococcus, streptococcus, pneumococcus, typhoid fever, tuberculosis, anthrax, smallpox, syphilis, and others) through the presence of the micro-organisms or of characteristic changes in the tissues of the fœtal organism. In many cases, for example, in tuberculosis and anthrax, the path which they have taken may be demonstrated since the placenta also shows characteristic pathological changes.

Up to very recently it has been assumed that besides a **placental transmission** there might occur also a **germinal transmission**, that is, an infection of the sexual cells before or during the fructification. Further, it has also been taken for granted, that, through infection of the fructifying spermatosome, an infection of the ovum without that of the maternal organism may occur, and such a mode of infection has been regarded as established, particularly in syphilis. Up to the present time

however, this mode of transmission has not been proved by unquestioned observations to occur in man and the mammals, and its occurrence even in syphilis has also been thrown into doubt (Matzenauer). According to our present knowledge we may say definitely that the transmission of infections through the placenta to the fœtus *in utero* has been positively demonstrated and occurs in different infectious diseases. Infections of the ovum or of the sperm before or during fructification are indeed possible, but it has not yet been positively demonstrated in the case of man and the other mammals that a further development into a viable fœtus is possible in the case of an ovum in which the agents of infection have produced characteristic changes. This is true not only in the case of acute infections, but also in such chronic ones as tuberculosis and syphilis.

According to the views of *Matzenauer*, in no case of hereditary syphilis can maternal transmission be excluded; and there are no clinical observations that speak for a pure paternal spermatic infection of syphilis. The fact that the mothers of children showing hereditary lues are immune toward syphilis (Colles' law) cannot be explained by the hypothesis that the mother has received syphilis toxins from the child syphilized from the father and in consequence has produced antitoxins (*Finger*), but can be explained only on the ground that she herself was infected with syphilis. That the mother often shows no syphilitic changes cannot be taken as an argument against the latter view, since syphilis may often be present with complete absence of symptoms.

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CHAPTER II.

The Spread and Generalization of Disease throughout the Organism. Autointoxications and Secondary Diseases.

I. General Considerations Concerning the Spread and Generalization of Pathological Processes in the Organism.

§ 19. If through the action of any injurious agent a local tissue-change is produced, there occurs first a **primary local disease** or **organ-disease,** which is accompanied by a disturbance of function of the affected part. If the injurious agent passes into the body-juices and into the blood without causing noticeable changes at the point of entrance, while within the body it gives rise to local changes, the resulting condition may be designated as a solitary or multiple **lymphogenous** or **hæmatogenous local disease** or **organ-disease.**

Local diseases may during their entire course remain confined to the organ originally affected, yet very frequently they lead to further **secondary diseases of organs** or to **a general disease.**

The *first method by which disease-processes spread* throughout the body is through *metastasis,* by means of which there are very frequently formed, not only solitary, but innumerable foci of disease throughout the body. Not infrequently there may occur such a *generalization of disease* by way of the blood and lymph-channels (tuberculosis, suppurations, and carcinomatous growths) that the majority of the organs will be found to contain metastases and show correspondingly more or less easily recognized functional disturbances.

A *second method* of the spread of disease occurs in those diseases in which in the primary foci there are formed toxic products which, taken up into the lymph and blood, produce such changes in different organs that they must be regarded as *intoxications by poisonous substances arising from diseased foci.* This intoxication is, as shown in § 12, of very common occurrence in the *infectious diseases,* and leads not only to *secondary degenerations of organs,* but much more to the picture of a more or less severe *general disease,* as shown by general disturbances of metabolism, fever, and disturbances of the central nervous system.

A *third form* of the spread of disease-processes throughout the body becomes possible by reason of the fact that the integrity and normal functional capacity of many organs are to a great measure dependent upon the function of other organs; and, further, upon the fact that the organism needs, for the preservation of its normal condition, the perfect functional working of its organs, and in the case of many organs cannot permanently dispense with their functions. There is, therefore, a large group of *local and general diseases which arise as the result of the imperfect functional activity of this or that organ.*

A *fourth mode* of origin of secondary diseases is through *autointoxication*—that is, through a *poisoning of the organism by substances which arise in the body itself through its own activity* (*metabolic poisons*). The *place of origin* of these substances is in part the intestinal tract (*enterogenous poisons*), and partly the tissues (*histogenous poisons*). The cause of the poisonous action of these products of metabolism lies partly in the fact that they are produced in an increased amount or are retained within the body as a result of disease of certain glands; partly also that they are not transformed to non-poisonous bodies, as is the case under normal conditions. In conditions of disturbed metabolism poisons foreign to the normal body may be produced.

A *fifth method* by which the animal or human organism may be injured is the production of symptoms of disease through the *impairment and loss of function of those glands producing an internal secretion* which is of importance to the organism. In this category belong especially the thyroid, hypophysis, pancreas, adrenals, liver, and sexual glands. Since in the disease of the glands just named intoxication plays also an important rôle, this group of processes is closely connected with that of the fourth mode of generalization of disease.

II. Metastasis and Embolism and Their Significance in the Etiology of Lymphogenous and Hæmatogenous Diseases.

§ 20. *The transportation, through the blood or lymph-stream, of a disease-producing agent, and the production of disease at the point of deposit of such agent*, is termed **metastasis**. This is one of the most common modes of the spread of disease throughout the body. Ordinarily the term metastasis is applied particularly to those cases in which the transportation of a given substance is followed by easily recognizable clinical and anatomical manifestations of disease, especially those of inflammation or tumor-formation, so that we are accustomed to speak of *metastatic inflammations* and *metastatic tumors*. There is, however, no good reason for not including also under metastasis those cases of transportation of corpuscular elements through the lymph or blood stream in which the changes produced by the transportation are less striking, and are recognizable only through a more careful anatomical or microscopical investigation.

The term metastasis indicates further that the substance deposited has arisen from some other known place within the body. If the source of the transported material is not known, or at least cannot be definitely located, we are accustomed to speak of **lymphogenous and hæmatogenous deposits and diseases.** The same designation is also applied to deposits of known origin.

The **significance of metastasis** is in all cases **dependent upon the properties of the transported body.** Insoluble bland foreign bodies of small size may have little effect upon the tissue; soluble and chemically active substances may, on the other hand, produce important tissue changes. Bacteria capable of reproduction may give rise to a disease which corresponds in general to that produced at the primary focus of infection. Tumor-cells capable of growth may develop into a secondary tumor. The **size** of the transported body is of essential importance in hæmatogenous metastasis, in that small bodies may pass all the blood-vessels, even the capillaries, while larger ones will be carried only through those vessels whose lumen is sufficiently large to admit them. When the latter have by any means obtained entrance to the arteries of

the greater or lesser circulation and are carried along by the blood-stream, they will become lodged at those divisions of the vessels where the vessel-lumen is too small to admit them, and will thereby more or less completely obstruct the vessel. This occurrence is designated by the special term **embolism**; the body blocking the vessel is called an **embolus** or a **vessel-plug** (Fig. 2, *b*, *c*). The effect of embolism is in general the more or less complete obstruction of the vessel, partly through the embolus itself, partly through an associated coagulation of the blood. As a result of such obstruction there is an interference with the circulation, which may vary greatly in different cases, in that behind the point of obstruction there may be established either a complete or partial compensatory circulation, or in other cases such a compensation may be entirely wanting. When the compensation is incomplete or wholly absent, the area of tissue supplied by the obstructed vessel undergoes degeneration or dies.

FIG. 2. Multiple emboli in the branches of the pulmonary artery, after thrombosis of the right auricle. *a*, Arterial branch; *b*, embolus; *c*, embolus with secondary thrombosis.

Both lymphogenous and hæmatogenous metastasis usually occur in the direction of the normal current, but under special conditions a transportation in the opposite direction may take place—**retrograde metastasis.** Such a change of current in the lymph-vessels occurs when the normal escape of lymph from the region involved is hindered through stoppage of the lymphatics, and the lymph is forced to seek other outlets. A similar condition may occur in circumscribed areas of the peripheral blood-vessels. In this way clots arising in the right heart or in the large veins of the body may be transported into the peripheral veins; particularly under conditions in which there occur backward waves of blood which gradually force the clots back into the smaller veins. According to the experimental investigations of Arnold upon dogs, foreign bodies (wheaten grits), which were too large to pass the capillaries, when introduced into the jugular or crural veins, as well as into the longitudinal sinus of the dura mater, were carried by retrograde metastasis not only into the main trunks, but also into the smallest branches of the veins of the liver, kidneys, heart, extremities, dura mater, pia mater, and orbit, as well as into the posterior bronchial veins.

In the case of a defect in the septum of the heart, bodies circulating in the blood may pass directly from one side of the heart to the other, and thereby give rise to a **crossed** or **paradoxical embolism.**

§ 21. **The substances which may be transported in the process of metastasis** may be conveniently divided into six groups, this classification being based partly upon the origin, partly upon the character of the transported body, and partly upon the effects of the metastasis.

In the first group are placed insoluble lifeless substances composed of very small particles, which enter the body from without, and which may be designated collectively as **dust.** The majority of these substances enter the body in the respired air, and pass from the lungs into other tissues. A smaller part may enter the tissues directly through accidental or intentional wounds (tattoo). Most frequently these substances are particles of soot, coal- and stone-dust, more rarely metal, porcelain, to-

bacco, hair or other kinds of dust. In tattooing of the skin, lampblack, india-ink, ultramarine, cinnabar, and other granular pigments are used.

The behavior of the tissues of the body toward such substances will be treated of elsewhere; it is only necessary to mention here that these forms of dust, sometimes in a free state, sometimes enclosed within cells, are deposited first in the tissues nearest the point of entrance, further in the lymph-vessels and lymphatic glands. In the latter location they may remain for a life-time; but in cases of excessive deposit they may be carried beyond the lymph-glands, especially in those instances in which the glands, because of the great deposit, undergo softening and give rise to inflammation and proliferation of the tissues in their neighborhood. Very often as a result of such changes the affected glands become confluent with and break into neighboring veins. This event is especially likely to happen at the hilum of the lungs, whereby the contents of the gland ultimately, sometimes slowly, at other times more rapidly, gain entrance to the vessel-lumen and are carried away by the blood-stream. In the case of the lungs, dust may be deposited directly in the vessel-walls and gradually penetrate as far as the intima. Further, the particles from a broken-down lymph-gland can again enter the lymph-stream, and, if not again arrested by some lymphatic gland, may reach

FIG. 3.—Fat-embolism of the lungs (Flemming's solution, safranin). *a*, Arteries filled with blackened masses of fat; *b*, fat-droplets in capillaries; *c*, veins; *d*, cells in the alveoli. × 100.

the blood-stream. It is also conceivable that softened lymph-glands may break directly into the thoracic duct.

As numerous experiments have shown, the dust gaining entrance to a blood-vessel remains but a very short time in the circulation. Large amounts artificially introduced into a vein disappear in a few hours from the circulating blood. The greater part collects in the capillaries of the liver, spleen, and bone-marrow, partly free and partly within leucocytes, in the former case adhering to the surface of the endothelium. After a short time the leucocytes containing the dust particles wander out from the vessels, so that the dust collects more and more in the tissues, where it is held for a long time, partly in wandering-cells, partly in fixed cells,

and partly free, and under certain conditions may remain here during the lifetime of the individual. In the mean time a part is carried in the lymphatics to other regions and there deposited, particularly in the portal and cœliac lymph-glands. According to the researches of Kunkel and Siebel, still other cells containing dust-particles may reach the surface of the body-cavities, either through the capillaries of the lungs, the parenchyma of the tonsils, and probably also from the lymphoid tissue of the intestines, and in this way be discharged externally. From the liver the dust-particles may be passed out in the bile. According to observations which may be not infrequently made on inflamed organs, wandering leucocytes are able to take up a great number of the particles lying in the tissues and transport them from the lungs, intestinal tract, and other organs to the surface, and in this way clear the tissues.

The second group is composed of portions of the body itself, which occasionally may be transported through the blood-stream; namely, **tissue-detritus, parenchymatous cells,** and **dead, coagulated,** and **broken-up constituents of the blood.** Of the elements arising from the destruction of tissue, **fat-droplets** (Fig. 3, *a*, *b*, and Fig. 4, *a*, *b*) most often find their way into the circulation; particularly when through trauma or some other pathological process, as, for example, hæmorrhage, the tissues are destroyed. This occurs most frequently in cases of crushing, destruction, and violent agitation of fat-tissue, as may happen in the case of the different panniculi adiposi and the bone-marrow; but fat may also enter the circulating blood through destruction of liver-tissue. The parenchymatous cells most frequently entering the circulation are *liver-cells, syncytial placenta-cells, portions of chorionic villi,* and *bone-marrow cells.* Ordinarily these are carried into the pulmonary arteries and capillaries, but through retrograde metastasis they may be carried into the veins, and through paradoxical embolism into the arteries and capillaries of the systemic circulation. Embolism of liver-cells and bone-marrow giant-cells is caused by traumatic and toxic injuries and hæmorrhages of the affected tissues. Placental-cell emboli, in the form of syncytial giant-cells, have been observed especially in puerperal eclampsia, but occur also in the course of normal pregnancies. Pulmonary emboli of small portions of the chorionic villi have also been observed. In diseased conditions of the intima of the heart or blood-vessels, *degenerated endothelium, broken-down and degenerated masses of connective tissue of the intima, portions of the valves,* and material of similar nature may gain entrance to the blood-stream. *Fragments* and *disintegrated portions of blood-corpuscles* may enter the circulation from hæmorrhagic foci or may arise within the vessels themselves, in the case of degenerative changes produced in the blood through the influence of various harmful agents. Coagulated *masses of blood* enter the circulation when a **thrombus**—i.e., blood coagulated in the vessels (see Chapter IV.)—breaks loose, either *in toto* or in fragments.

FIG. 4.—Fat-embolism of the kidney (Flemming's solution, safranin). *a*, Glomeruli with fat in the capillaries; *b*, fat-droplets in the intertubular capillaries. × 100.

The fate of the last-named substances is for the chief part dependent

upon their size and physical properties. All fragments of much greater diameter than the lumen of the capillaries become lodged in the bifurcations of the arteries (Fig. 2, *a*, *b*) and usually occlude the same. This occurs most frequently in the case of dislodged thrombi or of fragments of such; on the other hand, fat-droplets usually pass into the capillaries, where part remain, while others pass through and later become lodged in some other place. Since the fat occasionally passes first into the veins of the body and thence to the heart, the fat-droplets collect especially in the capillaries of the lungs (Fig. 3, *b*); but they may also pass through the lungs into the capillaries of the greater circulation, and are then found especially in the intertubular and glomerular capillaries of the kidneys (Fig. 4, *a*, *b*), and also to some extent in the capillaries of other organs. Capillary fat-embolism causes a noticeable disturbance of the circulation only when of extensive occurrence; in this case it may lead to the production of œdema of the lungs. Furthermore, the fat disappears in the progress of metabolism, or is conveyed into the neighboring tissues.

Parenchymatous cells (in so far as the entrance into the circulation of small living cells of the character of lymphocytes and myelocytes is not concerned) become lodged in the capillaries or smaller arteries in the case of arterial metastasis. The latter is especially true of liver-cells when entering the circulation *en masse*. At the place of lodgment their presence may lead to a heaping-up of blood-plates and a hyaline coagulation. The cells themselves do not multiply, but they may remain preserved for a certain length of time, according to Lubarsch, as long as three weeks. They then gradually die, the protoplasm dissolves, the nuclei swell or shrink, and finally lose their chromatin.

The point of lodgment of loosened thrombi or fragments of thrombi depends upon the path which they take, as well as upon their size. Since thrombi may be formed in the systemic veins, right heart, and pulmonary arteries, as well as in the pulmonary veins, left heart, and systemic arteries (see Chapter IV.), it is possible for embolism to occur in any of the arteries of the greater or lesser circulation. Very often the emboli lodge at the bifurcation of arteries, forming the so-called **riding** or **straddling emboli** (Fig. 2, *c*). Through retrograde metastasis emboli may be carried from the venæ cavæ or larger veins into the smaller veins. Defects in the septum of the heart may lead to the production of a paradoxical embolism.

Small fragments of thrombi, dead red blood-cells or fragments of such, endothelial cells undergoing disintegration or fatty degeneration, etc., meet the same fate as dust-particles. They may remain free or be taken up by cells; they are soon removed from the circulation and collect especially in the spleen, liver, and bone-marrow, where they undergo further changes and are destroyed. The products resulting from the destruction of red blood-cells may persist for a long time in the organs named, as colored deposits.

The third group of substances producing metastases is composed of **living cells**, which, originating from **proliferating tissue-foci** and having gained entrance to the circulation through direct rupture into the blood-vessels, or having entered the lymphatics, are carrried to other organs. This process may be observed in the case of **tumors** growing by infiltration. The metastasis of living cells from such a tumor leads through the proliferation of the transported tumor-cells to the production of **metastatic daughter-tumors**, which in the case of lymphogenous

metastasis develop first in the lymph-vessels and lymph-glands, but in the case of direct rupture into the blood-vessels arise in that part of the vascular system to which the tumor-cells are carried by the blood. The metastasis usually occurs in the normal direction of the blood- and lymph-streams, but *retrograde transportation* may also occur, whereby a tumor which has broken into one of the systemic veins may give rise to metastases in the region drained by smaller branches of other systemic veins. Retrograde metastasis is not infrequently observed in the lymphatic system, when closure of the efferent lymph-channels has produced a change in the direction of the lymph-current.

In the fourth group may be placed all those processes characterized by the entrance of **vegetable** or **animal parasites** into the circulation. If under such circumstances these organisms do not find conditions suitable for their development, they are quickly eliminated from the blood-stream and destroyed under the influence of metabolic processes. But if they are able to reproduce themselves anywhere, they will give rise to the production of **metastatic foci of infection,** which are located partly in the vascular system, but also partly extending thence into the neighboring tissues. The secondary foci in the case of bacterial invasion have in general the same character as that of the primary. If an embolus contains organisms capable of producing tissue-necrosis, inflammation, and putrid decomposition, there will occur, along with the embolism and the accompanying disturbances of circulation, suppuration and sloughing—that is, there will be a repetition of the same processes occurring at the original seat of infection.

As the fifth group of metastatic processes may be classed together those cases in which **constituents of the human body having undergone solution** are transported in the soluble state and again **deposited in a solid form**; and also those in which **extrinsic substances are taken up by the body in a soluble form** and are then **deposited in the tissues in a solid state.** Of the first class there occurs most frequently the entrance of bile-pigment into the circulation within the liver, so that this may permeate through the most varied tissues, and give to them a yellowish color (*icterus*). Not infrequently *iron-containing derivatives arising from the destruction of red blood-cells in the circulation* are carried to the spleen, bone-marrow, liver, and kidneys and form there pathological deposits of iron (hæmatogenous siderosis). *Fat* can be split off from the fat depôts in the form of soluble soaps and carried through the blood to different organs where it is again taken up by the cells and changed into neutral fat.

When preparations of silver are, for medicinal purposes, introduced into the body through the gastro-intestinal tract for long periods of time, there may occur a deposit of fine *granules of silver* in the connective tissue of the skin, in the glomeruli, medullary pyramids of the kidneys, intima of the large arteries, adventitia of the small arteries, in the neighborhood of mucous glands, connective tissue of the intestinal villi, in the choroid plexus of the cerebral ventricles, and in the serous membranes. Tissues showing such a deposit have a grayish-brown color.

The fact that the epithelial tissues and the brain are not affected shows that there is a selective action on the part of the tissues, and that this selective action differs essentially from that which is seen in the case of a metastatic deposit of corpuscular elements. It may therefore be assumed that the chemico-physical character and the functional activity of the tissues coming into contact with substances in solution exert a deter-

mining influence upon the separation and precipitation of such substances.

As a sixth group of metastatic processes may be classed the entrance of **air into the circulation.** If in any manner a large amount of air **gains entrance to the right heart,** an event which occurs especially in case of injury to the large veins lying in the neighborhood of the thoracic cavity, or more rarely from the opening of a vein, for example, of a stomach-vein, through ulcerative processes, the air mingling with the blood forms a foamy mass, which the contractions of the heart are scarcely able to drive onward. As a result the left heart receives little or no blood, the aortic pressure falls, and the affected individual quickly dies. Should the air enter the circulation in small amounts or intermittently, it may be carried by the blood-stream in form of air-bubbles and circulate through the entire body. Larger amounts may lodge for a time in the vessels of the major or minor circulation, obstruct their lumen, and cause disturbances of the circulation, which may give rise to functional disturbances of the brain and respiration. If these conditions do not cause death, the air is after a time absorbed.

If the lung-tissue be ruptured through trauma or through violent coughing, screaming, or vomiting, etc., **air may be forced into the connective-tissue spaces and lymphatics,** and may extend through these into all parts of the lungs, pleuræ, and the mediastinum, as well as into the skin. The conditions thus produced are termed *emphysema* of the skin, of the subcutaneous tissue, of the mediastinum, etc. Under certain circumstances the air may spread through a large area of the subcutaneous lymph-vessels and connective-tissue spaces, whereby the skin presents an inflated appearance and when pressed upon produces a crackling sound.

According to *Siebel* and *Kunkel*, granules of cinnabar and indigo injected into the blood-stream of a frog are quickly taken up by leucocytes, and after one to two hours no more free granules are to be found in the circulating blood. After twenty-four hours the leucocytes containing pigment-granules have disappeared from the circulation, and lie for the greater part clumped together in the capillaries, the greatest numbers being found in the capillaries of the spleen, liver, bone-marrow, and the lungs, while they occur in smaller numbers in the capillaries of the kidneys, and in still smaller numbers in the capillaries of the heart-muscle.

Even after two hours free pigment and cells containing granules are found outside of the vessels, and after a few days they have almost wholly disappeared from the vessels. The granules lie then partly in wandering-cells, partly in fixed cells, as well as in the free cells of the splenic pulp (*Ponfick*) and bone-marrow. They may be found in these organs for weeks afterward (*Hoffmann, Langerhans*). In both frogs and dogs some of the granule-containing cells find their way into the lumen of the alveoli and bronchioles and so pass out of the body. In the liver the pigment-particles for the greater part adhere for a short time to the endothelium of the liver-capillaries and may be taken up by the endothelial cells (*Browicz, Heinz*); another part is found in leucocytes, which later wander out from the vessels into the tissues. Thence they are for the greater part taken up into the lymphatics of the liver and ultimately reach the lymph-glands. A part of the granules finally pass out with the bile, but by what course they reach the bile-vessels is not known. In dogs the pigment-granules also collect in the tonsils and are carried to the surface through the epithelium by the leucocytes which have taken them up.

According to the observations of *Jadassohn* ("Pigmentverschleppung aus der Haut," *Arch. f. Derm.*, 24 Bd., 1892) and *Schmorl* ("Pigmentverschleppung aus der Haut," *Centralbl. f. allg. Path.*, 4 Bd., 1893), both normal and pathological pigment may be transported from the skin to the lymph-glands—in other words, a *pigment-metastasis* may take place.

According to *Lewin* (*Arch. f. exp. Path.*, 40 Bd., 1897), if the outflow of urine from the bladder be hindered, small foreign bodies can pass into the kidney-pelves, and thence into the urinary tubules, lymph-vessels, and veins, and into the general circulation.

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III. The Sequelæ of Local Organic Disease.

§ 22. **Secondary diseases which arise as the results of pathological conditions of individual organs** occur with great frequency as the result of *pathological changes in the blood and circulatory apparatus.*

The circulatory apparatus and the blood therein contained bear certain relations to all the body-tissues, and accordingly *diminution in amount* and *pathological alterations* of the blood, *as well as changes in the blood-vessels,* often give rise to diseased conditions of this or that tissue or of the entire organism. If the hæmoglobin-content of the blood is decreased through a diminution in number of the red blood-cells (oligocythæmia), or through a pathological condition of the same, or if the hæmoglobin through the action of carbon monoxide is rendered incapable of taking up the oxygen of the air, the body-tissues will no longer receive a normal amount of oxygen; consequently there will arise, in case the amount of oxygenation falls below a certain point, disturb-

ances of nutrition, as the results of which there occur very frequently conditions of fatty degeneration, and under certain circumstances death through paralysis of the nervous centres.

Should *an artery become narrowed or closed through thrombosis or embolism, or thickenings of its walls*, as in the case of the arterial disease known as *arteriosclerosis*, there will arise in the region supplied by the affected vessel a local deficiency of food-supply and oxygen, *local asphyxia*, and later *degenerative processes*, which frequently end in the death of the specific parenchymatous elements, at times also of the connective-tissue framework.

In the brain and spinal cord the vessel-changes lead to ischæmic processes of softening, which frequently result in paralysis, and not rarely in death. In the heart there results a diffuse fatty degeneration or local softening of the heart-muscle, giving rise to disturbances of cardiac activity or often even to complete insufficiency. In the kidneys the secreting glandular parenchyma, together with a portion of the connective tissue, undergoes necrosis or atrophy; and the loss of these substances gives rise to local or widespread contractions, which, according to their origin, are designated as embolic or arteriosclerotic atrophies.

In the stomach ischæmia of the mucous membranes gives rise to local ulcerations; in the liver and muscles to atrophic conditions. No tissue can withstand the harmful effects of a long-continued anæmia, and consequently the narrowing and closure of arteries, through the formation of clots or through changes in the vessel-walls, play a very important rôle in pathology; and are not only the causes of *anæmic necrosis* (see Chapter V.) and *hæmorrhagic infarction* (see Chapter IV.), but also of numerous *progressive atrophies of organs*. In the pathogenesis of the last named, arteriosclerosis has an especially important part, since in old age it is of very common occurrence, and gives rise to tissue-degenerations in organs of the most different structure. As evidences of such degenerative processes, the majority of the affected organs show later areas of scar-tissue, in which the specific parenchyma has disappeared while the connective tissue has increased.

The active participation of the vascular apparatus in all *inflammatory processes* (see Chapter VII.), the *disturbance of circulation* through the alteration of the vessel-walls, the *shifting and changes of the vascular channels* which result from the *closure of old vessels by proliferation of endothelium* or through *thrombosis*, as well as from the *formation of new vessels*, make easily comprehensible the fact that in all chronic inflammations the specific cells dependent upon a regulated nutrition undergo degeneration and are frequently replaced by connective tissue of a lower grade than normal.

A profuse watery discharge from the *intestines* may deprive the organism of water. If, as a result of stenosis of the œsophagus or pylorus, a sufficient amount of food is prevented from entering the intestinal tract, or if the stomach and intestine are no longer able to digest the food brought to them and to prepare it for assimilation into the body-juices, the organism as a whole becomes poorer in albumin and fat.

If the *heart* is no longer able to force onward with normal strength the blood coming to it, there will arise in various organs changes due to venous stasis. If the *respiration* is hindered or imperfect, the composition of the blood suffers changes. Collection of fluid in the thoracic cavity causes compression of the lungs; interference with expiration, with free inspiration, leads first to distention of the lung and later to

atrophy. If a part of the *lung* has been rendered useless by chronic inflammation, the inspiratory enlargement of the thorax affects only that portion of the lung which is capable of functionating, and this part becomes over-distended and in consequence finally atrophic.

Diseases of the parenchyma of the liver often give rise to disturbances of the circulation of blood through the organ, and stasis throughout the portal circulation with resulting ascites. Should the *pancreas* be destroyed or if it is no longer able to produce its ferments (proteolytic trypsin, amylolytic diastase, and the fat-splitting and emulsifying steapsin) there results an imperfect metabolism of albumin, carbohydrates, and fat.

Hindrance to the outflow of *urine* from the ureters renders difficult the secretion of the kidneys and leads to their atrophy. The loss of a *large portion of the renal parenchyma* is followed by increased blood-pressure in the aorta, increased action of the heart, and hypertrophy of that organ.

An *increased resistance in the pulmonary circulation* due to diseased conditions of the lungs is often followed by dilatation and hypertrophy of the right heart. *Obstruction to the flow of blood through the aortic opening* leads to hypertrophy of the left ventricle. Stenosis and insufficiency of the mitral valve cause a stasis of blood backward through the lungs to the right heart. This may be compensated for through hypertrophy of the right ventricle, or may extend farther back into the veins of the systemic circulation.

An *oblique position of the pelvis* leads to curvature of the spine. *Stiffness* and *immovability* of a joint cause atrophy of the muscles moving the joint, the atrophy being due to inactivity.

Diseases of the nervous system may give rise to functional disturbances and anatomical changes in any organ of the body—in glands, muscles, skin, bones, lung, heart, intestine, etc. These changes are to be referred partly to stimulation, partly to inhibition or arrest of nervous impulses, and partly to anæsthesia (anæsthetic tissues being especially liable to injury). Destruction of the large ganglion-cells in the anterior horns of the spinal cord leads to the atrophy of the corresponding peripheral nerves and muscles. Paralyzed extremities become atrophic. Diseased conditions in the region of the respiratory and vasomotor centres lead to disturbances of respiration and circulation. After injury to certain portions of the medulla oblongata, after concussion of the brain and spinal cord, through the presence of tumors in the brain, after psychical affections, after poisoning of the nervous system, there is caused under certain conditions a rapid withdrawal of the glycogen of the liver into the blood-stream and the excretion of sugar in the urine. Stimulation of peripheral nerves may produce abnormal reflex sensations and movements as well as circulatory disturbances in other parts of the body. Paralysis of both vagi or of their branches, the recurrent laryngeal nerves, through inflammatory changes or through pressure from neighboring lymph-glands, etc., may be followed by inflammation of the lungs, in that the accompanying paralysis of the laryngeal muscles favors the entrance of foreign bodies into the lungs during inspiration.

The so-called **trophoneurotic diseases of the tissues** are not mentioned above, for the reason that the trophic relations of the nervous system to the individual tissues are not yet clear, and the views of different authors as to the dependence of the tissues upon the nervous system vary greatly. Many authors ascribe to the trophic action of the nervous system a far-reaching influence upon the conditions of the tissues, and seek the nerves forming the connections with the nerve-centres, partly in the motor, secretory,

sensory, and reflex nerves, as well as in special trophic nerves. Thus, for example, muscular atrophy, glandular atrophy, atrophy of the bones and joints (in tabes and syringomyelia), different pathological conditions of the skin characterized by thinning, exfoliation of the epithelium, loss of hair, inflammations, etc., unilateral tissue-atrophies, necroses, also hypertrophic proliferations of muscles, glands, skin, or bones, etc., are all referred to affections of the nerves.

It cannot be doubted that both degenerative and hypertrophic tissue-changes and inflammations often occur as sequelæ to disturbances of innervation, but these most probably are not the direct result of the removal or change of nerve-influences affecting the tissues, but are rather the results of increased or decreased functional activity of the tissue, or of injuries, inflammations, or disturbances of circulation, which have developed in connection with the disturbances of innervation—for example, in connection with the loss of sensibility. *Golz* and *Ewald*, after completely destroying the thoracic and lumbar portions of the spinal cord of dogs, were able through great care to preserve uninjured the skin of the animals thus operated upon; they are, therefore, opposed to the theory of the existence of trophic centres and nerves.

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IV. Autointoxications and Disturbances of Internal Secretion.

§ 23. **Autointoxication** or **self-poisoning** may take place in a variety of ways. In the first place, *poisonous products of metabolism* of normal character and produced in normal amounts *may fail of proper excretion*, and, being carried over into the juices of the body, may be retained in the same. Secondly, the *physiological production of poisonous substances may be pathologically increased.* Thirdly, it may happen that *poisonous products of metabolism*, which normally are decomposed and thereby rendered harmless, may, as a result of a local or general metabolic disturbance, *escape such destruction.* Finally, it may also happen that, as *the result* of pathological changes or cessation of the functional

activity of certain organs, poisonous substances may appear in the blood and also in the urine. According to the place of origin poisons may be classed as **enterogenous**, arising in the intestine, and **histogenous**, arising in the tissues.

If **injurious products arising from the decomposition of albumin** *are retained or formed in excessive amounts in the intestinal canal,* they may give rise to both **local changes** and a **general intoxication.** For example, through the action of the bacteria present in the intestines, the *sulphuretted hydrogen,* arising from the sulphur of albuminous bodies, may be formed in such amount as to pass into the blood and impart its characteristic odor to the breath, and to be found also in the urine. Further, those toxic substances especially which arise from the decomposition of albumin through the action of the intestinal bacteria, when taken up into the blood are able to produce symptoms of poisoning, vomiting, headache, vertigo, stupor, acceleration and weakening of cardiac activity, etc. This action of toxins is especially marked in those cases in which there is fæcal retention or when the stomach or pancreas produces little or no enzyme, it being known that the enzymes have a neutralizing action upon certain toxins (see § 29). It is also probable that the tetany occurring rarely in dilatation of the stomach may be due to an autointoxication.

If the *function of the* **kidneys** *is disturbed to such a degree that the substances convertible into urea are excreted in insufficient quantity,* symptoms of intoxication may manifest themselves as the result of the retention of these substances. These symptoms are characterized by a condition of coma interrupted by convulsions and by disturbances of respiration—the symptoms collectively being designated as **uræmia.** According to von Limbeck, the retained substances have a narcotic action, the first effects of the narcosis being a dulling of sensibility and insomnia. It has not been yet been determined whether the toxic effects are due to a single element or to a mixture of substances. According to the investigations of Bohne, it is very probable that the retention of chlorides in the organism plays the most important part in the production of this condition. Besides the products of normal metabolism, those arising in the course of certain diseases (infections) may also have a toxic action.

Since many substances are excreted by way of the intestines, it is possible that under certain conditions a *disturbed function of the intestines* may render it difficult for the organism to rid itself of poisons and in this way lead to an autointoxication, **copræmia.** Likewise, an excessive *accumulation of carbonic acid* within the blood, through some interference with the exchange of gases in the lungs, may cause symptoms of poisoning.

When the *excretion of* **bile** *from the liver is hindered or arrested,* through some pathological condition in the bile-passages or in the liver itself, the elements of the bile are taken up into the blood, and the condition known as **cholæmia** is produced. Both the biliary salts and bile-pigment enter the blood, and their presence in the circulation gives rise to general lassitude, depression, mental exhaustion, inclination to sleep, slowing of the pulse-rate, itching of the skin, and abnormal sensations of hearing and taste. The effects upon the heart, muscles, and central nervous system are ascribed to the bile-salts. These also possess a hæmolytic action upon the red blood-cells. According to Bickel, ammonia-salts, leucin, and phenol must also be taken into consideration in the explanation of the symptoms.

If the **liver** has undergone marked pathological changes, not only does

the production of the bile as well as that of sugar and urea suffer, but certain substances brought to the liver from the intestines and normally decomposed by this organ may pass through it unchanged. Many believe that at least the severe symptoms (conditions of mental excitement, delirium, lethargy, coma, and cerebral paralysis) which occur in degenerations of the liver (icterus gravis) are to be referred in part to the presence of such substances in the blood, and base their belief upon the fact that under such conditions abnormal substances (ammonium carbonate) appear in the urine. In degenerations of the **pancreas**, large amounts of dextrose, acetone, and aceto-acetic acid (see § 25) may appear in the blood and urine. The two last-named substances have a toxic action, and many are disposed to ascribe such symptoms to a disturbance of pancreatic function. Finally, after degeneration of the **thyroid** or **adrenals** (§§ 25 and 26), pathological symptoms arise which possibly may be explained in part by the assumption that, as the result of the degeneration of these organs, poisonous products of metabolism are no longer destroyed.

In the constitutional disease known as **gout**, local deposits of metabolic products, in the form of **urates**, give rise to local tissue-degenerations and inflammations.

The condition of **eclampsia gravidarum** is an autointoxication resulting from pregnancy, and is probably due to poisons originating in the fœtal placenta.

The term **autointoxication** is not used with the same significance by all writers, many of them giving to it a broader meaning than the one given above, and even applying the term autointoxication to certain intoxications caused by pathogenic bacteria. In justification of such a view it may be said that the poisons in such cases arise for the greater part from component elements of the body. At the same time such a widening of the significance of the term appears to me inexpedient, in that the cause of the decomposition lies not in the body itself, but comes from without, so that the intoxication is the result of a preceding infection. It seems to me, therefore, to be more correct to apply the term autointoxication only to those forms of poisoning which are produced by products of metabolism, either under the influence of the activity of the body-cells or through the activity of bacteria constantly present in the intestine. As authorization for including the poisoning by products arising from intestinal decomposition among the autointoxications, I draw upon the fact that the intestinal bacilli which cause this decomposition are constant inhabitants of the intestine, and, according to the investigations of *Schottelius*, are indispensable factors in the processes of nutrition of man and the higher vertebrates. The *enterogenous autointoxications*, which are caused by these intestinal bacteria and which occur especially in childhood through retention of the intestinal contents (ileus) or in acute digestive disturbances (asthma dyspepticum), are in their severe forms characterized chiefly by disturbance of heart-action, small and frequent pulse, cyanosis, coldness of the extremities, sunken expression, and lowering of the body temperature. They may owe their origin in part to retention of intestinal contents in this or that portion of the intestinal tract, and in part to changes in the products of decomposition (formation of toxins) depending either upon the especial character of the material taken into the intestines (deficiency of carbohydrates, particularly of sugar, favors the extension into the small intestine of processes of decomposition normally confined to the colon), or upon a change in the virulence of the bacteria, or upon a deficient production of enzymes. It is not always possible in such cases to decide whether other bacteria, foreign to the intestine, are not also concerned in the production of poisons. The appearance of cystin in the urine is to be regarded, according to the researches of *Baumann* and *von Udranski*, as evidence of especial processes of intestinal decomposition resulting in the production of diamins.

The hypothesis that **puerperal eclampsia** is an autointoxication dependent upon pregnancy is at the present time supported by the majority of writers. Clinically the formation of toxic substances during pregnancy may be recognized by the occurrence of nausea, vomiting, emotional depression, chorea, hæmoglobinuria, albuminuria, and finally by eclampsia. The anatomical findings in women who have died of eclampsia are multiple thromboses in the smaller vessels and capillaries, and focal degenerations, usually associated with hæmorrhages in the liver, kidneys, brain, and lungs. In the

lungs there are also often found syncytial cells or portions of the chorionic villi. The fibrin-content of the blood is markedly raised. Should the child die (as takes place in about forty per cent of cases) corresponding changes may be found in its organs.

It was at first thought that the place of origin of the poison was in the maternal organism, and the cause was sought in alterations of proteid metabolism in which the disturbances of function were at one time located in the kidneys, at another time in the liver or in the thyroid. Recently the view has been advanced that the intoxication is to be referred to products of the placenta (cytotoxins). *Veit* assumes a direct intoxication through placental elements which takes place when the placental toxin can no longer be rendered inactive through the formation of antitoxin (syncytiolysin). On the other hand, *Arcoli* believes that the mother produces an excess of syncytiolysin and thereby poisons herself. *Weichart* thinks that there are formed through syncytiolysis, that is, the solution of the transported placental elements, albumin bodies (syncytiotoxins) which are poisonous to the mother. At the present time it cannot be decided which one of these hypotheses corresponds most fully to the actual conditions.

According to the view of *Bouchard*, autointoxications are caused in particular by leucomaïns—that is, by the earlier products of retrogressive metamorphosis of albuminous bodies, which normally are further decomposed in the process of intra-organic oxidation until they reach the form of urea and are then excreted.

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§ 24. If a gland produces an **internal secretion**—that is, if it gives to the lymph or the blood certain substances which are necessary for the normal performance of the functions of other organs or of the organism as a whole—an **alteration** or **total failure of this function** will cause more or less important disturbances of nutrition, as well as of the functional activity of other organs and of the entire organism. Such an internal secretion is ascribed to the liver, pancreas, thyroid, adrenals, thymus, and the sexual glands, yet our knowledge of the nature of these secretions is very slight and hypothetical. We are able to infer the influence exerted by these glands upon metabolism and the life of the organism only from the disturbances which arise when the glands in question become diseased. Among the most important of the diseases belonging in this category are *diabetes mellitus, thyreoprival cachexia, myxœdema, cretinism, Addison's disease*, and *the functional and anatomical changes occurring in the body after castration.* In a certain sense it is proper to consider in this connection *asphyxia*, which arises *from a failure of the lungs to perform properly their function,* in that through the functional activity of the lungs the requisite amount of oxygen is supplied to the organism.

Diabetes mellitus is a disease which is characterized especially by the presence of large amounts of grape-sugar in the urine (glycosuria), accompanied by a great increase in the total amount of urine secreted (polyuria), and often also by a pathological increase of acetone and the excretion of aceto-acetic acid and β-oxybutyric acid in the urine. At the same time grape-sugar and these acids are found in the blood and often lead to a diminution of its alkalinity. When the acid-content of the blood is high, headache, anxiety, delirium, fainting, and finally a condition of loss of consciousness (coma diabeticum) develop, and these conditions are probably to be ascribed to an acid-intoxication.

The entrance of sugar into the urine may be caused by too great an ingestion of sugar, so that part passes into the urine unchanged (alimentary glycosuria). Glycosuria may also follow an injury to certain portions of the medulla oblongata (puncture of Bernard), or as the result of disease-processes in the brain (degeneration, epilepsy, mental affections, severe psychical disturbances, tumors, parasites), or of certain forms of poisoning (carbon monoxide, curare, morphine, strychnine, amyl nitrite, nitrobenzole), in which the liver probably gives up its glycogen into the blood more rapidly than normal, so that a condition of hyperglycæmia is produced.

Finally, glycosuria may be due to an inability on the part of the kidneys to hold back the small amounts of glucose found normally in the blood, a phenomenon which may be produced experimentally by the

administration of phloridzin (von Mering) or of caffeine sulphate (Jacobj).

These alimentary, nervous, and toxic glycosurias are, however, to be distinguished from the ordinary form of diabetes, in that in the latter the cause of the glycosuria is to be sought, not in an increased conveyance of sugar into the blood, or in a pathological excretion of the sugar contained in the blood, but much rather in the fact that the diabetic patient is unable to decompose sufficiently the carbohydrates, and especially dextrose, while the sugars which turn polarized light to the left (levulose and inulin) ordinarily can be oxidized either wholly or at least in greater amounts than dextrose. In most cases the power to form fats from the carbohydrates is also lessened, yet there are cases in which this function is unimpaired and the sugars are stored up in the body in the form of fat (diabetogenous obesity).

According to the investigations of von Mering and Minkowski, which have been confirmed by different authors, this loss of power in the organism to oxidize the sugars brought into the body or formed normally in the body from albumin, or to store them up as glycogen or fat, is to be ascribed to an **insufficiency of pancreatic function.** This conclusion is drawn chiefly from the fact that after total extirpation of the pancreas in dogs, a diabetes of severe character, usually fatal within a few weeks, is produced, this being characterized, as is diabetes in the human subject, by polyuria, polydipsia, hyperglycæmia, glycosuria, diminution of the glycogen of the tissues, also at times by marked destruction of albumin, emaciation, excretion of large amounts of acetone, aceto-acetic acid, β-oxybutyric acid, and ammonia, as well as by the occurrence of a comatose condition. In support of the view that there is a definite relation between disturbances of pancreatic function and diabetes, it has been found that in certain cases of this disease in man the pancreas has exhibited demonstrable changes, of the nature of atrophy or degeneration. It should, however, be borne in mind that the anatomical investigation often fails to reveal a pathological condition of the pancreas; so that we are forced to content ourselves with the hypothesis that the anatomical changes underlying the functional disturbance of the pancreas are not demonstrable.

An exact explanation of the causal relations existing between pancreatic disease and diabetes cannot at the present time be given, yet from the foregoing experimental researches the hypothesis may be deduced that the pancreas produces an internal secretion which either gives the body the power to destroy glucose or increases this glycolytic capacity. Likewise, no explanation can at present be given for the increased destruction of the albumins and the accompanying abundant production of β-oxybutyric acid, aceto-acetic acid, and acetone. Since these substances are not always found in experimental pancreatic diabetes, their formation probably does not stand in direct relation to the excretion of sugar, but is to be regarded rather as a complication of diabetes (Minkowski). Their occurrence in diabetes, moreover, is not always constant, and they are found in other diseases (intoxications, carcinoma, disturbances of digestion).

The occurrence of *diabetes* after total extirpation of the pancreas is evidence that this organ possesses a special function which is of the greatest importance in the normal consumption of sugar in the organism. *Lépine* is of the opinion that there is in the blood a glycolytic ferment, which is formed by the pancreas and passed from this organ into the blood; and that the cause of the mellituria in diabetic patients and in dogs

from which the pancreas has been removed is to be sought in a decrease in the amount of this ferment. According to *Cohnheim, Rahel, Hirsch, Arnheim, Blumenthal,* and others the pancreas has the power, in a way not yet explained, of exciting to action the glycolytic ferments found in the different organs. The addition of pancreatic emulsion (*Cohnheim*) to the expressed juice of muscle increases its glycolytic capacity. At the present time it is impossible to offer a satisfactory explanation of the pathogenesis of pancreatic diabetes. According to Stoklasa the anaërobic respiration of the animal organs is an alcoholic fermentation caused by enzymes which may be separated from the cells and obtained in the form of powder. They will produce an alcoholic fermentation as long as they are not subjected to the action of lactic acid and thereby inhibited. In diabetes such an inhibition of the splitting of glucose into alcohol and carbonic acid occurs through the formation of lactic acid.

If only a portion of the pancreas of a dog be removed, no diabetes occurs, or at least the excretion of sugar is much less than after total extirpation (*Minkowski*). If in dogs from which the pancreas has been totally removed a portion of pancreas is transplanted subcutaneously, diabetes does not follow (*Minkowski, Hédon*), but occurs if the transplanted piece be excised.

According to *Minkowski*, there is no direct communication between the secretory function of the pancreas and that function of the organ concerned in the metabolism of sugar.

Poisoning with phloridzin produces, according to *von Mering* and *Minkowski*, a marked glycosuria in most animals and in man, and the same symptoms as those seen in diabetes, may be produced by a continuous administration of the poison. Since in this case the cause of the pathological excretion of sugar lies in the kidneys and represents a flushing-out of sugar from the organism, phloridzin diabetes cannot be identified with the ordinary form of diabetes found in man—that is, with pancreatic diabetes. In dogs in which diabetes has been produced by the extirpation of the pancreas, phloridzin produces an increase in the amount of sugar excreted (*Minkowski*).

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§ 25. **Cachexia thyreopriva** is a peculiar disease caused by *deficient or totally absent function of the thyroid*, resulting either from defective development or from pathological changes in the gland. To Kocher, who observed that it followed total extirpation of the thyroid, belongs the honor of having discovered the cause of this disease. Numerous clinical observations and experimental researches which followed this discovery have confirmed the fact that the presence of thyroid tissue is essential to the maintenance of the integrity of the organism, and that the body, especially during its period of growth, requires a thyroid gland capable of functionating normally. It is probable that the gland produces a substance (thyroiodine) which serves a useful purpose in the bodily metabolism. It is also possible that this gland neutralizes or destroys poisonous substances circulating in the blood.

FIG. 5.—Thyreoprival cachexia with cretin-like disturbance of development, in a man twenty-eight years old, arising after the total extirpation of the thyroid gland in patient's tenth year; length of body 127 cm. (See Grundler, *loc. cit.*)

According to experimental and clinical observations, the total extirpation of the thyroid gland produces in man and in animals, after a very short time, severe symptoms, which are characterized especially by muscular twitchings, convulsions, and paralysis, so that the condition has been called **thyreoprival tetany.** Young animals and carnivora are especially susceptible; dogs die for the greater part in a short time after total thyroidectomy.

If the loss of the gland is at first well borne, as is the case in man, there arise in the course of months or years peculiar disturbances of nutrition, beginning with weakness and heaviness of the limbs, feeling of coldness, often also pain and transient swelling of the limbs, with loss of mental activity, leading to a **cachexia** associated with anæmia, and characterized further by pale swellings of the skin, especially of the face (Fig. 5), and marked diminution of mental powers, together with a loss of muscular

strength, these symptoms finally terminating in death. The removal of the thyroid gland in childhood causes disturbances of growth, the increase in length of the bones falling below the normal or ceasing altogether (Fig. 5). Animals (rabbits and goats) that have had their thyroid glands removed soon after birth do not reach full growth and acquire an expression of stupidity.

In thyreoprival tetany the body temperature is increased; in the cachexia it is lowered.

Disturbances of thyroid function, as well as total extirpation, lead to pathological conditions of the body. Both clinical observations and experimental investigations tend to show that the peculiar disease (Fig. 6) known as **myxœdema** (Ord) is due to changes in the thyroid. Myxœdema is a condition in which the external appearance of the patient is suggestive of thyreoprival cachexia, in that the same characteristic pale and elastic swellings of the skin of the face (Fig. 6), not pitting on pressure with the fingers, are associated with similar pale and dry swellings in other parts of the body. Further, there is a loss of intellectual power, which finds expression in an increasing difficulty in thinking and acting, dulness of the tactile sense, retardation of muscular action, and a monotonous nasal voice. Finally, a marked general weakness and often also symptoms of actual mental derangement occur,

FIG. 6.—Myxœdema (case observed by *Meltzer*). Age of patient, thirty-seven years.

FIG. 7.—Myxœdema. The same individual (Fig. 6) after three months of treatment with pulverized sheep's thyroid.

and death follows a gradually increasing cachexia associated with symptoms of anæmia and coma.

Judging from the clinical and anatomical characteristics presented by the patients, **cretinism** (Fig. 8)—that is, the alterations in the structure and functions of the body which characterize this disease—is dependent upon disturbances of thyroid function. In support of this view is the fact that in cretins there is always present some degenerative condition of the thyroid, the organ being either enlarged (goitre) and changed in structure (endemic cretinism), or either imperfectly developed or wholly lacking (sporadic cretinism). Further, the general appearance of

cretins (Fig. 8) is similar to that of those individuals who as a result of thyroidectomy in early childhood (Fig. 5) have become stunted in development. The longitudinal growth of the long bones is more or less below that of the normal, while the soft parts are relatively well developed. The individual portions of the body are unequally developed, the head is relatively large, the abdomen and neck are thick, the bridge of the nose is depressed, while the nose itself is broad and stumpy; the skin is pale, flabby, wrinkled, and puffed, as if œdematously swollen, particularly over the face. The mental faculties are always feeble, sometimes markedly so. The power of speech and of understanding words may be entirely absent, and only the less-marked cases of cretinism are capable of performing work of any kind. The cause of endemic cretinism is unknown.

The great importance of the thyroid gland for the general nutrition of the organism, the cerebral functions, and the development of the bones has been placed beyond all doubt by numerous clinical observations and experimental investigations. As to the exact mode of action of the thyroid, there are, however, different opinions. If an animal, after thyroidectomy, is fed with the thyroid of some other animal—for instance, that of the sheep—the injurious effects usually observed after removal of the thyroid do not appear and will occur only when the feeding is stopped. In man the administration of fresh thyroid tissue or of thyroid extracts exerts a healing influence on the thyreoprival cachexia and myxœdema (Fig. 7); and reports have been published of favorable results of the same treatment in children suffering from cretin-like disturbances of development.

Fig. 8.—Female cretin, twenty-one years old; body-length 84 cm.; length of arm 30 cm.; circumference of skull 52 cm. (After Virchow.)

Goitres (enlarged and hypertrophic thyroids with nodules of new-formed thyroid tissue) which have not yet undergone secondary degenerations often diminish in size after the continued use of thyroid tissue for several weeks, often with a marked retrogression of the follicles (*von Bruns*), but after the cessation of the treatment soon begin to grow again.

According to *Lanz*, the extirpation of the thyroid in hens causes a diminution in size of the eggs; feeding with thyroid causes them to increase in size.

According to the investigations of *Baumann*, the thyroid constantly contains an iodine substance, **thyroiodine** or **iodothyrin**, which is present in the greatest quantity in old individuals, and in the smallest quantity in very young children. Iodothyrin for the chief part is usually combined in the thyroid with an albumin and a globulin body, but it may appear in a free form. The normal thyroid is able to store up the extremely small amounts of iodine brought into the body in vegetable foods or in the drinking-water, and to convert it into the combination mentioned above. The internal administration of preparations of iodine or the treatment of wounds with such leads to a greater accumulation of iodine in the thyroid.

According to *Baumann*, iodothyrin is the active element of the gland. Its employment in the treatment of goitres, myxœdema, and strumiprival cachexia, etc., has the same effect as the feeding with fresh thyroid tissue. It would appear that the organism requires iodine for its proper maintenance, and that the thyroid supplies it with the necessary iodine-combination. In regions where goitres are not commonly found (North Germany), the thyroid glands are, on the average, much smaller (from 30-40 gm.) and contain more iodine (on the average about 3½ mgm. instead of 2 mgm.) than in regions where goitres are numerous (Switzerland, South Germany). Whether the lack of sufficient iodine in the food and drinking-water is the cause of the hypertrophied condition of the thyroid in goitre, or whether some injurious agent, perhaps some lower organism, interferes with the specific function of the gland, cannot be said at the present time. Among the domestic animals having an especially large amount

of iodine in the thyroid are the sheep, the cow, and the calf, while in hogs the iodine-content of the gland is small.

Blum regards the thyroid as an organ whose function it is to destroy enterotoxins arising from the decomposition of albumin in the intestine.

Anatomical investigations have failed to throw any definite light upon the question of the internal secretion of the thyroid. It has been proved that the colloid produced by the thyroid cells passes into the lymph-vessels. It is probable that iodothyrin is contained in this colloid substance. During intra-uterine life the thyroid appears to be destitute of its function, which in later life is so important.

It is also possible that Basedow's disease (Graves' disease, exophthalmic goitre), which is characterized by a pulsating goitre, exophthalmos, rapid heart, tremor and great excitability on the part of the patient, is dependent upon a disease of the thyroid —namely, a *hypersecretion* (*hyperthyreosis*). In support of this theory lies the fact that the glands of such patients are rich in functionating gland-tissue, but no positive conclusions concerning this point can be drawn at the present time. According to *Beebe* the experimental feeding of thyroid glands produces symptoms and metabolic changes similar to those of Basedow's disease. Removal of a considerable portion of the gland will in many cases effect a cure; and the recurrence of the disease after operation is in most cases accompanied by a recurrence of the tumor. *Oswald* has shown that the colloid of the glands from cases of exophthalmic goitre is, in the majority of cases, deficient in iodine. He believes that the symptoms are due to an overflooding of the body by an excess of a less potent secretion. *Beebe*, *Rogers*, and others have attempted to treat cases of exophthalmic goitre with a specific serum, but it is yet too early to judge of the value of such treatment. *Ewing* has studied the histological changes in the glands of forty cases of exophthalmic goitre, and believes, in common with other writers, that the histological findings are to a certain extent specific. An extensive cellular hyperplasia with large areas of imperfectly formed alveoli interspersed with giant cells and resulting in nearly complete loss of colloid appears not to occur except in connection with the nervous symptoms of Graves' disease. Some writers regard the thymus and parathyroids as associated in some way or other with the pathogenesis of exophthalmic goitre, but no definite proof of this is at hand. The removal of the parathyroids in young carnivora is followed in a few days by symptoms more or less like those of Basedow's disease. Thyreoprival tetany has also been ascribed to the disease or removal of the parathyroids. *Halsted* has reported cases of *hypoparathyreosis* following removal of the human parathyroids, the symptoms being restlessness, insomnia, attacks of flushing, and numbness. The feeding of fresh parathyroids caused some improvement. Transplantation of the parathyroids into the thyroid and spleen has been successfully carried out experimentally.

According to the investigations of *Rogowitsch*, *Stieda*, and *Hofmeister* the extirpation of the thyroid in rabbits leads to a hypertrophy and altered structure of the **hypophysis.** It would appear that the rôle of the latter organ in the animal economy is in some way correlated with that of the thyroid. Tumors of the hypophysis have been repeatedly observed in giantism and acromegaly.

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§ 26. **Addison's Disease** is a peculiar affection, usually fatal after a course of about two years on the average, and is very probably to be regarded as the result of a *functional disturbance of the suprarenals.* It is characterized chiefly by the appearance of a light-yellow-brown to dark-brown, diffuse, and spotted pigmentation of the skin (*melasma suprarenale*), which shows itself first in the portions of the skin normally exposed, later in other parts of the body-surface and in the mucous membrane of the mouth. Even at the beginning of the disease, or even before the pigmentation of the skin, there occur loss of appetite, nausea, pain in the epigastrium, diarrhœa, constipation, and vomiting—all symptoms of a disturbed intestinal and gastric function; later, muscular weakness; and finally, nervous symptoms, asthenia, fatigue on slight exertion, headache, vertigo, fainting, epileptiform attacks, and coma. Occasionally a recognizable increase of the pigment of the skin does not occur, and the disease is characterized only by the gastro-intestinal symptoms, progressive weakness, and anæmia.

In about eighty-eight per cent of all typical cases of Addison's disease the suprarenals are found to be diseased, in the majority of cases being changed into a caseous or fibro-caseous mass. More rarely there are found tumors in the adrenals or simple atrophy, agenesia, or hypoplasia. There can scarcely remain any doubt that the disease of the suprarenals bears a causal relation to the symptoms described above; it may, therefore, be designated as a **suprarenal cachexia.** In what way the loss or change of the function of the suprarenal bodies acts injuriously upon the organism cannot at present be stated. It is not improbable that the suprarenal bodies, like the thyroid, produce a substance which is necessary for the preservation of the organism; or possibly poisonous substances are destroyed by them.

A **normal functional activity of the adrenals** is necessary to the integrity of the organism. This is based not only upon clinical observations and anatomical investigations in man, but also upon animal experiments. For example, the extirpation of the adrenals in dogs, rabbits, cats, and guinea-pigs gives rise to a lowering of blood-pressure, muscular weakness, and nervous symptoms, paralysis, coma, and, if life be sufficiently prolonged, a loss of strength. According to the observations of different writers the adrenals appear to have an influence upon the growth of the body. In defective development of the adrenals or in degeneration of these organs occurring in early life an abnormal smallness of the body has been observed; in tumor formations of the adrenals leading possibly to an increased functional activity giantism has been noted (*Linser*). The administration of adrenal extract causes in animals an increase of blood-pressure, slowing of the pulse-rate, increase in the strength of muscle-contractions after nerve-stimulation, and a decrease in respiratory movements. The cause of the increase of blood-pressure is regarded by some as the effect of the extract upon the vasomotor centre (*Scymonowicz*), by others as a direct action upon the heart and the arterial walls (*Schäfer*). The contraction of the small vessels has been definitely proved.

The active principle of the adrenals obtained by different methods has been put upon the market in two different preparations, *adrenalin* and *suprarenin.* When injected into the tissue or applied to the mucous membranes in strong solution, $\frac{1}{10}$ pro mille, they produce anæmia through the contraction of the vessels and can be used with good success in connection with local anæsthetics. In toxic doses adrenalin produces dyspnœa, diminished sensibility, lowered reflexes, impairment of voluntary movements, and finally paralysis. Diabetes may also appear after the injection of adrenal extract. According to *Loeper* and *Crouzon*, a temporary reduction in the number of red blood-cells takes place.

Since anatomical changes in the adrenals have not been found in every case of Addison's disease, many attempts have been made to refer the disease to other local changes, particularly to pathological conditions of the sympathetic and the sympathetic ganglia. But the anatomical findings offered to support this view are not sufficient for such an interpretation. That in a small number of cases the adrenals appear to

be unchanged cannot, even if all the cases of this kind were diagnosed properly (which was probably not always the case), be taken as an argument against the pathogenic significance of adrenal degeneration, since an apparently normal adrenal may functionate abnormally.

According to *Ciaccio*, *Wiesel*, and others, the active substance of the adrenals that contracts the blood-vessels is produced by the cells of the medullary portion of the adrenal (the cortical portion is regarded as an organ whose function it is to neutralize or destroy poisons). Chromaffinic cells occur also in the tissues of the sympathetic nervous system, and it has been claimed that in Addison's disease the destruction of the chromaffinic cells plays the most important rôle. On the other hand, other writers (*Karakascheff*) are of the opinion that the disease or loss of the cortical substance of the adrenal is of importance in the pathogenesis of Addison's disease. Cases of destruction of the medullary portion through hæmorrhage with subsequent calcification of the necrotic mass, without any symptoms of Addison's disease, may be regarded as proofs favoring this theory.

§ 27. As a pathological condition due to the loss of a specific glandular function should be classed also those abnormal symptoms in the structure and functions of the body resulting from **castration**—that is, the removal from the body of the sexual glands. If the ovaries are removed from a woman after the age of puberty, menstruation usually ceases at once, but rarely only after some time. Sexual desire and the erethism accompanying the sexual act are usually diminished in intensity, but may also be unchanged. The remaining portions of the genital apparatus undergo atrophy; this is especially marked in the case of the uterus. Certain nervous manifestations may follow, the most common of which are excitement, with reddening and heat of the skin, especially of the face, often associated with attacks of sweating; these symptoms being of most frequent occurrence in the period immediately following the castration. The disposition remains unchanged or may become more cheerful, especially in those cases in which the woman is by the castration relieved of severe pain. At times depression or melancholia may follow. If the ovaries are removed or destroyed during childhood, the secondary sexual characters are not clearly defined; the muscles are more strongly developed, the development of the pelvis is changed, and the breasts do not increase in size.

Castration in an adult male produces no marked change in the build of the body. On the other hand, if boys are castrated, the build of the body loses in masculine character. There occurs an increased deposit of fat, particularly on the abdomen, while the musculature is only feebly developed. The external genitals remain small, the prostate is diminished in size, and there is no growth of beard or pubic hair. The larynx remains small, and the voice is child-like. The mental powers are lacking in energy and strength.

In castrated stags, the antlers are not developed; in cocks the combs, wattles, and ear-lobes do not reach normal development, while the feathers are developed to a greater extent (*Selheim*). In oxen, the horns and the nipples develop to a greater extent than in the bull.

According to *White*, *Kirby*, *Kummel*, *Bruns*, and others, castration in fully developed animals causes a decrease in the size of the prostate; and it is said that, in old men suffering from prostatic enlargement, castration may lead to a diminution in size of the enlarged prostate. Others (*Czerny*, *Socin*) express a less favorable opinion as to the results of castration in such cases.

In what manner the *extirpation of the sexual glands affects the entire body* has not been determined with certainty. By many authors it is assumed that, as a result of castration, the trophic influence exerted upon the tissues by the sexual glands, through the nervous system, is withdrawn. The cessation of the menses may indeed be regarded as due to the withdrawal of nervous stimuli, and the atrophy of the uterus may

perhaps be dependent upon the same cause; but in general it is more likely that certain *chemical substances* (oöphorin and spermin), which exert a certain influence on the functions, growth, and development of the body, are formed in the sexual glands.

According to the investigations of *Loewy* and *Richter*, after castration of female dogs there occurs a lowering of the oxidation-power of the cells of the body and a decrease in the amount of oxygen used by about twenty per cent. According to *Breuer* and *von Seiller*, the total mass of hæmoglobin and red blood-cells is diminished. The administration of dried ovarian substance or of oöphorin from the ovaries of the cow or hog to the animal operated upon causes an increase in the amount of oxygen consumed even greater than the average observed before the castration. Preparations of testicles showed no such influence. In male dogs the same conditions prevailed; spermin caused only slight increase in the gaseous interchange, oöphorin gave a marked increase (as much as forty-four per cent).

Zoth and *Pregel*, who have carried out experiments with reference to the effects of glycerin extracts of the testicles of animals, report that injections of this extract increase very markedly the power of muscular contraction.

According to the investigations of *Born* and *L. Fraenkel* the *corpus luteum* appears to possess an internal function. On the one hand, it is thought to govern the metabolism of the uterus and to make possible the insertion of the impregnated ovum in the uterus, and, on the other hand, to excite menstruation.

The **thymus** has also been credited with the function of an internal secretion, and the condition of *lymphatic constitution* (*constitutio lymphatica*) has been ascribed to disturbances or loss of this function.

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V. Fever and Its Significance.

§ 28. When a local organic disease takes on the character of a **general disease**, or when a disease at its very inception manifests such a character, there is seen very frequently a *symptom-complex* which is designated as **fever**. Particularly in the case of those infectious diseases associated with symptoms of intoxication does the appearance of fever during their course play an important rôle. The characteristic sign of fever is an *increase of bodily temperature;* but accompanying this there are other symptoms, especially an *increase of the pulse-rate, disturbances in the distribution of the blood, changes in the gaseous interchange within the lungs,* and also *changes in the urinary secretion.* There is usually also a

subjective feeling of illness, but this is not a necessary part of the symptomatology of fever, but an especial effect of an infection associated with symptoms of poisoning, the infection occurring at the same time with the feverish increase of temperature, or before it, or even after it.

Observation of the normal body has taught us that, in spite of changes of temperature externally and also of changes in other extrinsic conditions, the body-temperature is maintained at an average height of 37.2–37.4° C. (98.96–99.32° F.). The absolute variation between morning and evening is 1–1.5° C. (1.8–2.7° F.), the maximum occurring at evening.

The elevation of temperature of the body above that of its surroundings is due to the fact that through chemical changes occurring in the organism, particularly in the muscles and glands, heat is produced, and to such an extent that the temperature of the body may be raised one degree

FIG. 9.—Temperature-curve of a continued remittent fever, with slowly rising and gradually falling curve (typhoid fever).

Centigrade (1.8° F.) in half an hour. This phenomenon of heat-production is offset by one of heat-dispersion, occurring chiefly through the skin, lungs, and the excreta. Both heat-production and heat-dispersion are under the influence of the nervous system, and through its regulation of both processes a constant temperature is maintained.

On exposure to lower temperatures the heat-production is increased (chiefly through the agency of the muscles), while heat-dispersion is lessened through contraction of the cutaneous vessels and inhibition of perspiration.

On exposure to higher temperatures heat-dispersion is increased through increased frequency of respiration, dilatation of the arteries of the skin, and increased secretion of sweat.

In those conditions which we call **fever** there is a *disturbance of the regulation of heat-production and heat-dispersion*, in favor of heat-production, so that the *temperature of the body is more or less elevated above the normal* (Figs. 9–11). Elevations of temperature (rectal measurements) to 38° C. (100.4° F.) are called *hypernormal;* from 38° to 38.5° C. (100.4–101.3° F.), *light fever;* from 38.5 to 39.5° C. (101.3–103.1° F.), *moderate fever;* 39.5–40.5° C. (103.1–104.9° F.), *marked fever;* over 40.5° C. (104.9° F.) (evening temperature), *high fever;* and over 41° C. (105.8° F.), as *hyperpyrexia.*

Four **periods** may be distinguished in fever. The first, which is known as the **pyrogenetic** or **initial stage or stadium incrementi**, corresponds to that time during which the previously normal temperature reaches the average height characteristic of the disease. This period is sometimes short (Fig. 10), half an hour to two hours long, and in this case is usually accompanied by a *chill;* sometimes longer (Fig. 9), one to several days, and then usually runs its course without a chill, though chilly sensations may repeatedly occur.

In the second period, known as the **fastigium**, whose duration varies according to the disease from a few hours to several weeks, the temperature reaches one or several *acme-like highest points*, between which there are more or less marked remissions.

In the stage of **decline of the fever** or the **defervescence** or **stadium decrementi**, the body-temperature returns again to the normal. If this takes place through a rapid fall of temperature (Fig. 10), it is called **crisis**; if slowly, it is termed **lysis** (Fig. 9). The former is usually accompanied by profuse sweating, and in a few hours, or at most in one to one and a half days, the temperature falls two or three degrees, occasionally as much as five to six degrees Centigrade. In lysis the temperature falls gradually for three to four or more days; the decline may be either continuous or intermittent.

FIG. 10.—Temperature curve of a continued fever with rapidly ascending and rapidly falling curve (pneumonia).

FIG. 11.—Temperature-curve of an intermittent tertian fever (malaria).

The boundary-line between fastigium and defervescence is not always sharply defined, and before the latter sets in there may occur elevations of temperature, this phenomenon being called **perturbatio critica**. If between the fastigium and defervescence there occur several days of uncertainty with striking fluctuations upward or downward, such period is known as the **amphibolous stage**. Occasionally there may occur a short period in which the temperature is somewhat lowered, but yet remains high above the normal, to sink after a few days to the normal either rapidly or by a gradual decline.

In the stage of **convalescence** the temperature returns to the normal condition. The heat-regulation is during this time still imperfect, so that often slight elevations and not infrequently subnormal temperatures occur.

If during the course of a fever the daily variation is slight, so that the difference between maximum and minimum is not more than that under normal conditions, the fever is called a **continuous fever** (*febris continua*) (Fig. 10). If the differences are greater, the fever is termed **subcontinuous** (*febris subcontinua*), **remittent fever** (*febris remittens*) (Fig. 9), or **intermittent fever** (*febris intermittens*) (Fig. 11).

In the last-named, **afebrile** periods (*apyrexia*) alternate with periods of fever, each *paroxysm* having an initial period, a fastigium, and a defervescence. In the infectious disease known as **febris recurrens** there is first a continuous fever, which after a few days falls by crisis; after about a week or so a second rise of temperature occurs, which may be followed by a second stage of apyrexia, and this by a third period of fever.

Many diseases—such as typhoid fever, pneumonia, measles, relapsing

fever, etc.—are characterized by a typical temperature-curve; others—as pleuritis, endocarditis, diphtheria, tuberculosis, phlegmon, etc.—have no typical course of fever.

The **elevation of the body-temperature** in fever is dependent primarily on an *increase in heat-production through increase of the chemical changes occurring in the body.* The *respiratory interchange of gases*—the excretion of carbonic acid and the taking-up of oxygen—is increased, a proof that the oxidation-processes and with these also the heat-production are increased. At the same time the *excretion of nitrogenous elements in the urine* (urea, uric acid, creatinin) *is increased*—on the average about from seventy to one hundred per cent, under certain conditions even as much as threefold. There is also an increased destruction of the albuminoid substances of the body, the albumin of the organs, even in the latent period of the fever.

The increase of heat-production varies in different fevers, but in general does not reach that degree which can be produced by excessive muscle-action and over-feeding with albumin. It is at its highest point at the time of the initial chill, in that the violent muscular contractions thereby produced may increase the production of heat.

The second cause of the elevation of the body-temperature is *deficient heat-dispersion.* At the height of the fever the patient as a rule gives off more heat than the normal individual, but this dispersion is not sufficient to offset the excessive heat-production. Heat-production is constantly increased; heat-dispersion is irregular.

In the initial stage the cutaneous vessels are contracted as a result of stimulation of the vasomotors, the skin is pale, the heat-dispersion slight, under certain conditions even less than normal.

Chills occur when, through the contraction of the peripheral arteries, the supply of blood, and consequently the heat-supply, to the cutaneous nerves is suddenly diminished, while in the interior of the body the temperature is rising.

In the **second stage of fever** the skin is often hot and reddened, and in certain diseases sweating occurs; but the increased heat-dispersion thereby produced is not sufficient to lower the temperature to the normal. The increased excitability of the vasomotors or the deficient irritability of the vaso-dilators is also present during this period, and as a result the skin-temperature, as well as the heat-dispersion, varies greatly. The skin is at times pale and cold, at other times red and hot, and the hands may be cold while the trunk is hot. The centres governing heat-dispersion are therefore acting faultily.

In the **period of defervescence** the relations of heat-dispersion and heat-production are changed in favor of the former. The cutaneous vessels become dilated, the skin gives out a great amount of heat from the abundance of blood circulating through it, and when the critical fall of the fever occurs there is usually profuse sweating.

The **cause of fever** is not known with certainty, yet this much can be said, that fever is most frequently the *result of the entrance of a harmful agent into the fluids of the body.* In many cases this harmful agent arises demonstrably from a local focus—for example, from erysipelatous and phlegmonous inflammations of the skin. Experimentally, fever may be produced by very different procedures—for example, through the infusion into the vessels of an animal of blood from one of another species, through the injection of animal or vegetable substances that are beginning to decompose, and through numerous infections. In man, the *infec-*

tious diseases, which are regarded as due to specific micro-organisms multiplying in the body, are in particular characterized by fever.

It is probable that the parasites multiplying within the body cause an increased tissue-destruction, either directly or through the production of unformed ferments, and that at the same time substances are produced which act as *poisons* upon the central nervous system. The action of the latter may be assumed to be of such a nature that, on one side, the activity of the muscles and glands, and consequently the heat-producing metabolism, are increased; while, on the other hand, through the diminished and disturbed functions of the nerves governing sweating, as well as of the vasomotors, the processes of heat-dispersion fall behind those of heat-production. Further, though the organism makes an effort to regulate the temperature, it is no longer able to maintain it at the normal level, because of the disturbances of the regulating apparatus. What share in the increase of body-temperature is due to the direct action of bacteria and of the ferments formed by them, or what share is due to the increase of metabolism, through the stimulation of the nerves as well as by disturbance of heat-dispersion, cannot at present be determined. It is, however, certain that the factors vary in different cases. That under certain conditions, changes in the nervous system without contamination of the tissue-juices are in themselves sufficient to cause a feverish increase of temperature, is shown by the fact that fever may occur in epileptic attacks, in the periods of excitation occurring in the course of progressive paralysis, after severe frights, after the passage of a catheter into the bladder, etc. According to the investigations of Richet, Aronsohn, and Sachs, a marked increase in body-temperature with increase of the respiratory interchanges of gases and increased excretion of nitrogen (Aronsohn and Sachs) may be produced in animals by a puncture which passes through the cerebral cortex and strikes the corpus striatum. The same phenomenon may be produced also by electrical stimulation (Aronsohn, Sachs) of the same portion of the brain. Nevertheless, fevers dependent upon nervous disturbance are rare, and are overshadowed in importance by those caused by infection.

The rise of temperature in fever is usually accompanied by an **increase in the frequency of the pulse-rate**; but in some cases this effect of the elevation of temperature may be so greatly modified through stimulation of the vagus—as, for example, in basilar meningitis—that the pulse-rate may be lowered. The pulse is at one time full and bounding, at another time small because of weakened contractions of the heart.

The impairment of the contractions of the heart-muscle is dependent partly upon the constant high temperature, partly upon poisonous substances, which are produced by the morbid processes peculiar to the especial disease, and which exert a harmful influence upon the muscle-substance of the heart or upon the nervous system.

In diseases accompanied by fever there is usually a marked sensation of illness with a heavy feeling in the head. In severe fevers there occur clouding of consciousness, symptoms of excitation and depression, hallucinations, delirium, apathy, involuntary evacuations, tremors of the hands, convulsions (in children), etc. The muscles of the body become weak and not infrequently painful. Digestion is decidedly impaired; the appetite for food is slight, but on the contrary there is great thirst; the mouth is dry. There is an increased frequency of respiration; after the appearance of muscular weakness the respiratory movements are superficial. The excretion of urine is usually diminished; the amount

of urea in the urine is increased, while that of sodium chloride is diminished.

In prolonged fevers there is marked wasting of the body, in that a large portion of the albuminous material and fat of the body is destroyed.

To what extent these symptoms in individual cases are dependent upon the increase of temperature or to what extent upon the damage to the organism caused by the specific morbid process, it is difficult to say, but the marked effects upon the nervous system must for the greater part be regarded as a result of the infection and intoxication.

Death results most often from cardiac insufficiency, but it may be brought about also by the severity of the infection and the intoxication, by the wasting of the ~~strength, as well as by an excessive elevation of~~ temperature to 43°, 44°, or 45° C. (109.4°, 111.2°, and 113° F.). It should, however, be remarked that under certain conditions very high temperatures may be borne for a length of time without fatal results, and that the death following very high temperatures cannot be ascribed to the abnormal temperature alone, but is rather to be regarded in part or wholly as the result of the infection (see § 3).

The questions concerning the nature of fever, which *Galen* designated as *Calor prœter naturam*, have been much advanced during the last decades by numerous clinical and experimental investigations. From these we have learned of the associated disturbances of metabolism, the increased consumption of oxygen, the increased excretion of nitrogen and carbon compounds, as well as of the disturbances of the heat-dispersion. If we, in spite of this knowledge, do not yet possess a full understanding of all the morbid processes which in a given case may cause fever, we may attribute this to the fact that the *causa efficiens* of fever is not a single entity, but may be one of many different factors, and that the feverish elevation of the body-temperature does not always occur in exactly the same manner. The increase of the tissue-changes and oxidation-processes within the body is not always brought about in the same way. Further, the disturbance of heat-dispersion through radiation from the skin and the evaporation of water is not always the same, but changes, not only in the course of one febrile disease, but also in different forms of fever. Correspondingly, the rôle played by the nervous system in the occurrence of the feverish increase of temperature is not the same in every case. According to *Aronson*, the essential feature of fever is a pathological increased stimulation of the heat-centres whereby the motor-trophic apparatus of the body muscles is excited to an increased production of heat and to changes in the heat-dispersion. The different types of fever are determined by the different kinds of stimuli, which in the infectious diseases are especially manifold. The foundation type is an elevation of the body-temperature in the absence of any other disease of the body, and caused solely by a direct mechanical, electrical, or chemical stimulation of the heat-centre. According to *Senator*, there is, in fevers, no harmony between the regulation of heat and metabolism; and we must therefore assume that heat is developed through other processes than those leading to the production of urea and carbonic acid. According to *Herz*, heat is set free by the changes in the arrangement of the molecules of the cell-protoplasm, which occur in many of the cells in fever patients, and which lead to the destruction of protoplasm. Further, heat may be liberated by processes of swelling and coagulation of the protoplasm, while at the same time the diminished activity of the regenerative processes in fever occasions a loss in the storing-up of latent heat. On the other hand, *Krehl* and *Matthes* are of the opinion that oxidation forms the sole source of heat.

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CHAPTER III.

The Protective and Healing Forces of the Human Body. The Acquiring of Immunity.

I. The Natural Protective Contrivances, Protective Forces, and Healing Powers of the Human Organism, and their Action.

§ 29. The human organism is not entirely defenceless against the many harmful influences to which men during the course of their lives are exposed. It possesses various **protective contrivances** and **protective forces**, by which it is able in many cases to ward off the injurious agent, or at least rapidly to counteract its harmful influence, so that a disease may be either wholly prevented or confined to a slight local lesion of much less severity than the disease usually produced by the particular injurious agent. As the mode of action of different injurious influences varies greatly, so does the manner of defence likewise vary greatly. The protective forces may act at very different times—that is, sometimes even before the tissues have been damaged, at other times after the injurious action has reached a certain stage, and threatens, either through direct extension or through metastasis, or through poisoning of the body-fluids, or through disturbance of function, to spread further through the body.

When the environment of the body becomes relatively cold or relatively warm, those *regulating functions* are brought into play through which the organism can *increase or diminish heat-production and heat-dispersion*, and in this manner protect itself within certain limits against the influence of the external temperature. If these regulating functions are imperfectly performed, as in consequence of alcoholic intoxication, the individual may more easily die from the effects of cold than when under normal conditions.

We cannot speak of special protecting contrivances against gross *mechanical influences*; yet it is to be noted that the tissues by virtue of their physical properties are fitted to offer resistance to numerous forms of traumatism without receiving injury. If small, firm bodies, such as dust-particles, reach the mucous membrane of the respiratory or intestinal tracts, the *epithelium* forms a protective barrier against their entrance into the tissue-spaces. Further, if ciliated epithelium is present, the dust-particles may be carried away by the *movements of the cilia*, or they may become surrounded by the *mucus* produced by the epithelium and mucous glands, and in this way are transported out of the body.

Not infrequently there appear cells on the surface of the mucous membrane which encompass the dust-particles, and, taking these up into their substance, are carried away with the secretion of the mucous membrane. This phenomenon, known as *phagocytosis*, is observed on the mucous membranes of the pharynx and respiratory tract and in the alveoli of the lungs. The active agents participating in it are not only

the wandering-cells which pass from the tissues to the surface, and are derived chiefly from the blood-vessels and also from the nodes of lymphadenoid tissue in the mucous membrane, but epithelial cells as well. The peculiar phenomenon of phagocytosis depends upon the fact that the cells can, by movements of their protoplasm, take up little particles, which, like insoluble dust, exert no harmful influence upon the cell-protoplasm. If these cells laden with dust pass outside of the body, the taking-up of the dust by the cells appears to be a useful activity which aids in the cleansing of the organs from dust. If the dust-laden cells, on the other hand, as happens particularly in the lungs, pass into the lymph-channels and are deposited along their walls or are carried to the lymph-glands—that is, if a metastasis of the dust-containing cells into the internal organs takes place—the taking-up of dust by these cells appears in a less favorable light; and we can regard this act as a useful phenomenon only through the consideration that the infiltration of the pulmonary connective tissue and lymph-glands with dust is less harmful than the deposit of dust on the inner surface of the alveoli.

When dust-particles, free or enclosed in cells, reach the *lymph-glands*, they are arrested and deposited in the cells of these glands, so that the lymph-glands may be regarded as trustworthy *filters*, which guard the blood and the internal organs from the entrance of dust.

Against the *action of poisons* the human body is able to protect itself in various ways. In the case of corrosive poisons the *horny layer* of the epidermis and the *mucus* of the mucous membranes offer a certain protection; and under certain conditions a marked increase in the production of mucus — in the stomach, for example — may greatly diminish the harmful effects of a corrosive fluid. Through a transudation of fluid from the blood-vessels on to the surface of the mucous membrane a caustic fluid may be so diluted as to modify its action. On the other hand, the injurious substance may be thus spread over a greater surface, and thereby cause a more widespread damage to the tissue.

On many poisons, abrin, ricin, the toxins of cholera, tetanus, and diphtheria, and snake-venom, the digestive juices have such an influence that doses invariably fatal when injected under the skin may be borne with impunity when taken by the mouth. According to Ransom, guinea-pigs are able to withstand, when administered by the mouth, an amount of tetánotoxin equivalent to three hundred thousand times the minimal fatal dose. According to Nencki and others, this *neutralization of the poison is produced by the digestive enzymes*, at one time chiefly through the pepsin, at another time through the trypsin and the mixture of the pancreatic juice with the bile. It is probable (Nencki) that the digestive enzymes cause a slight change in the molecules of the toxin, similar to the change of albumin into albumose; and the products arising from the toxins may accordingly be termed *toxoses* or *toxoids*. The intestinal enzymes have no neutralizing influence in the case of sausage-, meat-, fish-, bean-, pea-, etc., poisoning produced by the *Bacillus botulinus;* and, therefore, after the eating of such infected foods severe and fatal intoxications may occur.

In the case of those poisons which after their entrance into the body-juices act injuriously upon the blood or the nervous system, a favorable counter-action on the part of the organism may be given partly by a *rapid excretion of the poison* through the kidneys, liver, intestine, pancreas, salivary glands, mammary glands, sweat glands, and lungs; partly through their *transformation into combinations soluble with difficulty*, which

are thus stored up in different organs (liver), and partly *through a change of the poisons into combinations that are relatively harmless and easily soluble*, which are then taken up into the circulation and excreted, and partly through a *chemical change of the poison.*

Of *natural immunity against poisons or natural resistance to poisons* we know but little at present, yet there is no doubt that many poisons are poisonous only for certain organisms, and it is probable that man is resistant to many poisons which are injurious to certain animals. The same thing holds true especially of the toxins (§ 11), such as are formed by bacteria or by higher animals (snakes) and plants (ricin and abrin). If we consider that many animals are only slightly or not at all susceptible to poisons which have marked action upon the human body—for example, the hedgehog is immune or resistant to cantharidin and the bite of poisonous snakes respectively; birds are immune against atropine and opium; goats against lead and nicotine; while dogs, rats, or other animals used for experiment show a disproportionately greater resistance to bacterial poisons or plant-alkaloids than does man—so it is very probable that the reverse is also true. The natural immunity of man against many of the infectious diseases of animals must depend upon a resistance to the toxins produced by the particular bacteria. According to Ehrlich, this resistance to poisons may be explained by the theory that the particular toxin possesses no chemical relationship to any one of the body elements. A relative immunity may therefore depend upon the fact that the healthy individual possesses already a certain amount of antitoxin (for example, against diphtheria toxin).

Fromm has recently briefly summarized our knowledge concerning the *chemical protective resources of the animal body in intoxications. Inorganic poisons* are rendered harmless chiefly by three kinds of chemical action—oxidation, reduction, and combination with a protective body with liberation of water. Phosphates and sulphides are oxidized so that phosphoric acid and sulphuric acid arise which are neutralized and excreted. The iodates and chlorates are changed into the easily soluble and less poisonous iodides and chlorides which are then excreted. The metallic salts and metallic oxides are converted into albuminates (the salt-like combination of metallic oxide and albumin) or into sulphides. Inorganic acids are combined through alkalies and changed into less poisonous salts.

Organic poisons are transformed into non-poisonous substances through oxidation, reduction, the liberation or the taking up of water. Often several reactions follow one another; usually the product arising through oxidation or reduction is combined to one or more other substances with the liberation of water. Such protective substances are represented particularly by the sulphates arising through the disintegration and oxidation of albumin, by glycocoll arising in the breaking down of albumin, glycuronic acid arising through the oxidation of the carbohydrates, and perhaps also urea.

Poisonous acids of the fat series are oxidized to carbonic acid and water. Phenol and those bodies which through oxidation pass directly into phenol are through a combination with sulphuric acid made soluble, harmless, and capable of being excreted; for example, phenol is excreted as potassium-phenol-sulphate; benzoic acid and its oxidation products and those substances that are transformed directly into benzoic acid or their derivatives are combined by glycocoll; trimethyl carbinol, naphthol, and chloral hydrate appear in the urine combined with glycuronic acid, chloral hydrate after its transformation into trichlorethyl alcohol.

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§ 30. Against the **infections and intoxications caused by parasites** the human organism possesses various **protective contrivances** and **powers of defence**; and these play a very important rôle in the diseases caused by bacteria. In the first place, man possesses a **natural immunity** against many of the micro-organisms pathogenic for animals (for example, swine plague, swine-erysipelas, cattle-plague, symptomatic anthrax), so that the given micro-organisms are not able to reproduce within the body, either because they do not find in human tissues the necessary conditions of life, or because the presence of certain chemically active substances hinders their increase or kills them directly. Further, immunity may also rest upon the simple fact that the poisons produced by given bacteria in a given organism are inactive because no chemical affinity or relationship exists between the poisons and any one of the body elements. **For the protection of the body against the pathogenic micro-organisms there are available certain protective forces,** which, according to their action, may be divided into four groups: the first hindering the entrance of bacteria into the tissues; the second hindering the unlimited local spread of those bacteria which have gained entrance and have begun to multiply; the third preventing the entrance of bacteria into the blood and their metastasis; the fourth hindering intoxication, or at least weakening it, and reducing it to a low degree.

For the **prevention of the entrance of pathogenic bacteria into the tissues** the same properties of tissues are effective as those hindering the entrance of dust; and in such capacity the *protective epithelium* and the *mucus* play a very important rôle. In the respiratory tract the *movements of the ciliated epithelium* also furnish protection, and in the stomach the *poisonous action of the gastric juice* upon many pathogenic bacteria is an efficient means of defence. There can be no doubt that many pathogenic bacteria are not able to penetrate into the tissues, not only through the uninjured external skin, but also through an unwounded mucous membrane, without some assistance favoring colonization and reproduction, and that the stomach secretion not infrequently hinders the activity of the bacteria (pneumococcus, cholera spirillum), or even kills them.

It appears also that the mucus secreted by the mucous membranes not only can envelop the bacteria, hinder their entrance into the tissue, and favor their removal, but that—what is of much greater importance—the mucus acts upon the bacteria, causing them to degenerate, either in that it contains substances which are injurious to the bacteria or in that it offers an unfavorable medium for the growth of the bacteria. In this way, according to Sanarelli and Dittrich, pus-cocci, cholera-spirilla, and pneumococci gradually lose their virulence and die in the mucus of the mouth-cavity, while diphtheria-bacilli and tubercle-bacilli apparently are not injured by mucus. In the secretions of the vagina and uterus, various kinds of bacteria likewise soon die.

In the intestine the *bacteria* normally present there (B. coli communis, B. lactis aërogenes) afford an effective protection against the multiplication of any pathogenic bacteria that may happen to be present; for example, against diphtheria and tetanus bacilli and against cholera-spirilla, while,

on the other hand, the development of staphylococci and streptococci does not appear to be hindered by them.

Not every pathogenic organism, therefore, which gains a foothold upon the skin or upon any of the accessible mucous membranes or gains entrance into the intestines or the lungs produces an infection. It has been shown through repeated investigations that in normal individuals there not infrequently occur in the upper respiratory passages and mouth-cavity not only harmless bacteria—i.e., those which cannot reproduce in human tissues—but also those which can undoubtedly produce disease, as, for example, cocci which cause suppuration or those which are able to cause croupous inflammation of the lung. It must, therefore, be granted that bacteria which are found upon the mucous membranes and have perhaps multiplied there often die and are carried away without having produced infection. This occurs especially in the case of the cocci above mentioned, and tubercle-bacilli, as well as in the case of cholera-spirilla which suffer when brought into contact with the acid secretions of the stomach. Finally, it may also be assumed that of the pathogenic bacteria entering the alveoli of the lung in the inspired air, many do not reproduce, but die.

When **bacteria have succeeded in gaining entrance locally and have begun to multiply**—no matter whether they have passed through the epithelium without the aid of any other influence (typhoid-bacilli, cholera-spirilla), or whether they have passed into the connective tissues through the medium of small wounds (tetanus-bacilli, pus-cocci, tubercle-bacilli)—if they produce further effects either through local destruction of tissue or through the poisoning of the fluids of the body, there may be brought into action on the part of the body certain **counter-influences** *which either hinder the further development of the bacteria or weaken or even completely destroy the poisons produced by them.* The first-named restraining influence must naturally depend upon local conditions, either upon vital tissue-processes or upon the effects of chemical substances.

As previously mentioned, the development of bacterial colonies gives rise to local tissue-degenerations, inflammation, and tissue-proliferations —all of which are processes in which the amount and composition of the fluids found in the affected region, as well as the cells themselves, are changed. Since in some of these cases a destruction of the bacteria has been observed, and the infection not infrequently comes to an end through the complete disappearance of the bacteria, the death of the latter must be regarded as dependent upon local conditions.

Many writers ascribe the **prevention of the further spread of the infection** and the **destruction of the bacteria**, in local foci of growth, to the activity of cells which collect at the seat of infection and take up the bacteria into their protoplasm—that is, to **phagocytosis** is ascribed the most important rôle in the protection of the body against bacterial invasion. According to Metschnikoff and others, the amœboid cells of the body carry on a fight against the foreign invaders and endeavor to overcome them and destroy them. Such a characterization of the phenomena of phagocytosis is not supported by the actual facts, and can be regarded only as a poetical manner of expression by which consciousness and will-power are attributed to the amœboid cells of the body (the leucocytes and the proliferating tissue-cells)—which attributes it is evident do not exist. Scientifically considered, the gathering of the cells at the infected focus and the resulting phagocytosis represent simply an expression of certain processes which are natural to the amœboid cells, and which are

dependent upon the fact that the cells under the influence of mechanical, chemical, and thermal influences perform certain definite movements. We know through numerous investigations that the motile cells of the body are in part attracted, in part repelled or paralyzed by means of chemical substances in certain concentrations of solution (see the Chapter on Inflammation); and, further, that contact with hard bodies can stimulate them to the sending-out of protoplasmic processes.

Such phenomena are designated as **negative** and **positive chemotropismus** or **chemotaxis** and as **tactile irritability**. We must assume that the bacteria multiplying within the tissues act upon the amœboid cells through the chemical substances which they produce, sometimes repelling or paralyzing, sometimes attracting, in the latter case affording conditions favorable for phagocytosis. The bacterial proteins arising from the bodies of dead or dying bacteria and passing over into solution in the body juices have, in particular, a positive chemotactic action upon the phagocytes.

The *result of the taking-up of bacteria into cells* depends in a particular case partly upon the properties of the devouring cells, partly upon the properties of the microparasites, and can result as well in the death and dissolution of the parasite, as in the death of the cells; or in a symbiosis of the cells with the parasites, the latter living within the cells unchanged and giving rise to no disturbance. In the first-named case the phagocytosis may be regarded as a curative process which hinders the multiplication and spread of the bacteria. In the second and third cases, on the contrary, the phenomenon is useless for the prevention of the spread of the parasites; indeed, there are cases (leprosy and to some extent also tuberculosis) in which the parasites find favorable conditions for development inside of the cells, increase within them, and finally cause their destruction. If the cells containing bacteria remain preserved for a length of time, they may wander with the enclosed bacteria to other parts of the body, in this way effecting a metastasis.

Phagocytosis is therefore only of slight significance as a protective force in a certain number of cases; yet it cannot be doubted that the phagocytes in certain infections take up, not only dead or dying, but also living bacteria not yet injured by other agents, and can cause their death. The collection of great numbers of cells in the infected tissue may, through the *close packing of the lymphatics*, offer a certain *mechanical hindrance* to the spread of bacteria, yet the protection so afforded is frequently insufficient.

If bacteria, either free or enclosed in cells, pass from the lymph-vessels into the **lymph-glands**, the latter act as **filters**, as in the case of dust, and retain the bacteria; but the protection which they offer is sufficient only when the bacteria so collected in the lymph-glands are hindered in their reproduction and are killed by the influence of their surroundings. The destruction may be accomplished under the influence of phagocytosis, but *in many cases phagocytosis is possible only when the bacteria are weakened or have already been killed.* Further, the taking-up of living bacteria by the cells is not always followed by destruction of the bacteria, but there very frequently takes place an intracellular multiplication of the bacteria.

More important than phagocytosis for the prevention of the spread of bacteria and other microparasites is the influence exerted by certain **chemical substances** in solution in the tissues. Since the saprophytic, non-pathogenic bacteria, when injected into living tissue, are killed

within a very short time, we must assume that *in the tissues there are present chemically active substances which are poisonous for many bacteria and can cause their rapid destruction.* Further, since many pathogenic bacteria ordinarily increase only locally (tetanus-bacilli, diphtheria-bacilli, cholera-spirilla) and after a certain time perish within the infected area, without spreading further through the body, it is very probable that *the tissues of the body also contain* **substances which are poisonous for many pathogenic bacteria** and prevent their spread. The phenomena observed in local infections speak also for the fact that such substances at times are formed in increased amounts or are aided in their action by newly-formed poisonous substances. It is, furthermore, probable that the crowding of cells which takes place in the infected tissue or in its neighborhood leads also to an increase in the production of these poisonous substances, and may thereby hinder the spread of the bacteria; nevertheless, attention should be drawn to the fact that in many infections the spread of bacteria through the tissues comes to a standstill in places where there has been no crowding together of cells. It is also a fact that in many infections the spread of bacteria through the body by metastasis is either wholly wanting (tetanus, diphtheria) or at least is insignificant in comparison with the local infection, and is usually followed by relatively insignificant local changes. The explanation of this fact is to be sought, not so much in the assumption that local tissue-changes, through the formation of special chemical substances or through the aid of mechanical substances or through the aid of mechanical hindrances—such as that afforded by a wall of cells—hinder the entrance of bacteria into the lymph and blood, but much more in the fact that *there are present in the lymph and blood itself certain forces which are able to injure and weaken the bacteria* taken up into these fluids or to destroy them. (See paragraph below on **opsonins.**)

The **hostile action of the blood on bacteria** has been ascribed to the phagocytic action of the leucocytes; and this theory is supported by the fact that such a phagocytosis can be demonstrated very frequently in acquired infections or after the artificial introduction of bacteria into the blood; and, further, by the fact that the bacteria within the blood, enclosed in cells, may often be carried out of the blood-vessels and deposited in different organs—for example, the spleen, liver, ~~bone-marrow, and~~ the kidneys—and there destroyed or excreted from the body. These observations do not warrant the conclusion that phagocytosis forms a protection against the spread of bacteria in the lymph and blood; indeed, in those very cases in which a transportation of bacteria through the blood does not take place, phagocytosis is also absent; while on the contrary, the entrance of bacteria into the blood, and the multiplication of the same inside of the blood-vessels, is very often accompanied or followed by phagocytosis. Here, again, phagocytosis is of the nature of a secondary phenomenon which occurs when there are present in the blood bacteria or protozoa, that are not able to prevent themselves being taken up into the bodies of the leucocytes—that is, they exert a positive attraction on the phagocytes.

When bacteria are taken up by cells, they either die or continue to multiply inside of the cells, according to their properties and their condition at the time of the phagocytosis.

The forces which are able to hinder the development of bacteria in the *blood* are believed by the majority of writers to depend upon the presence of **antibacterial chemical substances,** which are designated

alexins (Buchner) or *mycosozins* (Hankin). According to Buchner, with whom the majority of authors are in harmony, there is formed a ferment-like body, an **enzyme** (*cytase* [Metschnikoff]), which, through the aid of an intermediate body (amboceptor), exerts its destructive action upon the bacteria. *The leucocytes themselves are probably the chief producers of this protective body*, and the leucocytosis observed in the blood in the course of many infections may therefore increase the protective power (see **opsonins** below).

So far as conclusions can be drawn from the behavior of the human and animal organisms in infectious diseases, we may assume *that in the blood of man there are always present protective chemical substances, that is, alexins*, particularly so against bacteria which never or only exceptionally enter the blood; and *that others, on the contrary, are produced only during the course of an infection*, so that not until a certain stage of the infection does an inhibition of the development of the bacteria, through the formation of antibacterial substances, occur. In favor of such hypothesis speaks the fact that many bacteria (typhoid-bacilli, cholera-spirilla, pus-cocci) possess at first their full virulence when distributed through the body by the blood, but later suffer a loss of virulence and finally die.

The **means of protection** which the organism possesses **against the poisons produced in the tissues by bacteria** are to be found, first, in the possibility of a rapid **excretion of the poisons** by the kidneys, or, under certain circumstances, also by the stomach, intestine, and skin; and this action may in certain cases suffice to prevent a fatal poisoning. Further, in certain infections in which true toxins are formed there is an antagonistic action on the part of the organism, in the sense that these poisons are made ineffective through the action of **counter poisons**, the so-called **antitoxins**. (See § 31 and § 32.)

The *antibacterial properties of the blood and lymph* against certain bacteria have been demonstrated conclusively by the experimental investigations of various writers. These experiments have shown that the bactericidal action of the blood of a given animal is exerted only upon certain forms of bacteria and never upon all; and that this action is subject to individual variations.

According to the investigations of *Fodor*, *Petruschky*, *Nuttal*, *Ogata*, *Buchner*, *Behring*, *Nissen*, *Pansini*, and others, the blood and the serum from dogs, rabbits, and white rats are capable of rendering the anthrax-bacillus harmless, and even of killing it; but this action is a limited one, so that after the introduction of a large number of the bacilli into the blood taken from the vessels, the bacilli after a time begin to multiply. Defibrinated blood of dogs and rabbits can destroy the cholera-spirillum and typhoid-fever bacillus; but, on the other hand, has no effect upon the different pus-cocci, and against proteus; the same is true also with regard to the blood-serum. Human blood or blood-serum can kill typhoid-bacilli, diphtheria-bacilli, and the bacilli of glanders.

Von Baumgarten and *Walz*, as well as *A. Fischer*, oppose the view that there are chemically active substances in the blood, and explain the natural immunity of the tissues and the blood against certain bacteria as due wholly to the inability of the bacteria to find there the necessary chemical conditions for growth and multiplication. They regard the fact that different bacteria which have been passed into the blood or blood-serum do not develop at all, or show but partial or delayed growth and a great diminution in numbers when cultivated upon plates, as in no manner speaking for the presence of bactericidal substances in the blood. According to their view, the second transplantation into another culture-medium causes a disturbance of the processes of assimilation and osmosis. There arise in consequence plasmolytic changes in the bacteria present in the serum; during the pouring of the plates the already injured cells die from disturbances of assimilation. On the other hand, it is to be noted that *A.* and *H. Kossel* have demonstrated that certain products of animal cells (nucleinic acid, protamine) possess bactericidal properties.

The **alexins** of the blood serum are made inactive through heating to 55° C., and are very susceptible to the action of sunlight (*Buchner*), and they can also be

destroyed by living bacteria and their decomposition products. They resist pepsin. The addition of salt to the serum lowers their sensibility to heat. By means of a 90-per-cent sodium sulphate solution there may be obtained from dog serum a precipitate which remains active when dried at 70° C.

The **bactericidal action** finds its analogy in the **globulicidal** and **hæmolytic action** of the **serum;** that is, its capacity to destroy and dissolve the red blood-cells of an animal of a different species.

According to the investigations of *Ehrlich* and his students the **bactericidal** and **globulicidal antibodies** contain *two components*, one *thermolabile*, which is destroyed by heating to 55–60° C., and a *thermostabile*, which resists heating. Both must act together in order to bring about the death of bacteria or the dissolution of the red blood-cells.

Ehrlich designates the thermostabile component as the *immune body* or *intermediate body* (*Bordet* "as the substance sensibilatrice"), the thermolabile as the *complement* (earlier designated the addiment). To the immune body he ascribes two *haptophorous side-chains*, one the cytophile, which unites with the cell (bacterial cell, red blood-cell), for which it possesses a chemical affinity, and a *complementophile*, which combines with the complement. It is therefore an *amboceptor*, which carries over the action of the complement to the cell. Buchner's *alexin* is identical with the thermolabile component, the complement of Ehrlich (*Bordet*). That a union of the immune body with red blood-cells and bacteria, respectively, does take place has been demonstrated by the investigations of *Ehrlich, Morgenroth, Hahn, Trommsdorff, von Dungern,* and others.

Hankin, Kanthack, Denys, Hahn, Löwit, and others assume, on the ground of experimental investigations, that the *alexins are produced by the leucocytes. Kossel* holds it as possible that the nucleinic acid present in the leucocytes in relatively rich amounts plays a rôle in the destruction of the bacteria. *Noesske* believes that the eosinophile cells of the bone-marrow in particular produce bactericidal substances. It is not possible at the present time to draw a definite conclusion as to the part played by the colorless cells of the blood in the defence against infections.

According to *Bitter, the bactericidal substance found in organs*—that derived from the lymph-glands, spleen, and thymus—is to a certain extent different from that of the blood and the blood-serum, and therefore does not originate wholly in the blood. It is certain that the bactericidal action of the blood is not the only protective influence which can oppose the spread of an infection, or wholly prevent it, and confer immunity.

According to observations of *Czaplewski*, anthrax-bacilli in an infected organism, which have been taken up into leucocytes, degenerate as a rule more slowly than those lying free in the blood and tissue-juices. It appears, therefore, as if under certain conditions the cells afford to the bacteria which they enclose a certain degree of protection from the bactericidal substances of the tissue-fluids.

The *antitoxins* which render the bacterial poisons harmless are usually formed first during the course of the infection; but, according to the investigations of *Wassermann, Abel, Fischl, von Wunschheim,* and others, the serum of healthy men also contains such substances. Serum which contains the antitoxin against a certain toxin—as, for example, that against the diphtheria-toxin—can be a good culture-medium for the given bacteria; the antitoxin does not destroy the bacteria.

Animals refractory toward diphtheria contain in the blood serum no diphtheria antitoxin, but according to *Wassermann* about 80 per cent of human individuals have in their blood a not insignificant amount of antitoxin. The immunity of the animals depends therefore not upon the presence of the antitoxin, but on a lack of affinity between the poison and the tissue-cells (*Ehrlich* and *Wassermann*). It is possible to produce in mice a fatal intoxication with the blood of apparently healthy fowls that have been injected with large doses of tetanus toxin.

Opsonins. The protective function of phagocytosis has in recent years been accorded a position of great importance through the discovery by *Wright* and *Douglas* (1902) of the presence in the blood and other fluids of the body of certain substances, called by them *opsonins*, which render various bacteria susceptible to the phagocytic action of leucocytes. It is now apparently an established fact that certain special substances, normal and immune, act upon the bacteria and change them in such a manner that they are readily taken up by polynuclear leucocytes *in vitro*. Opsonins capable of acting upon a variety of bacteria occur in normal blood. They appear to be the most important antibodies in infections with streptococci, staphylococci, pneumococci, micrococcus melitensis, gonococci, meningococci, the bacilli of plague, dysentery, anthrax, tuberculosis, typhoid fever, the colon bacillus, cholera spirillum, etc. Whether this wide range of opsonic action is dependent upon a common opsonin or upon a variety of specific opsonins is not yet determined. Specificity of the opsonins probably does not exist. Various researches suggest that they may be a constant

quantity. They are to a certain extent thermolabile, being partly destroyed at 60-65° C. Bacteria first treated with normal serum and then exposed to this temperature are taken up as under normal conditions. The opsonic power of the blood is increased in recovery from infection, and it can also be artificially increased by immunization with living attenuated bacteria, dead bacteria, or proteid constituents of the bacterial cells. The **opsonic index** is the relative influence of a patient's blood upon phagocytosis as compared with that of normal individuals. It is determined by mixing in a capillary tube equal parts of the patient's serum, a suspension of leucocytes, and an emulsion of the bacteria against which the index is taken. Control tests are made in the same way with normal serum. The mixtures are incubated for a time, thin smears are made, dried, and stained, and the average number of bacteria taken up by the leucocytes is estimated. Regarding the index of the normal blood as unity, the average number of bacteria in the leucocytes of the patient's serum divided by it will be the opsonic index. 75–100 leucocytes are usually counted. A low opsonic index is taken as indicating the presence of an infection or of a low degree of resistance to it, while a high index indicates a high degree of resistance to a recovery from infection.

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§ 31. **The healing-powers of the human body** *are furnished by those life-processes which are able to compensate for the disturbances and changes caused by disease, and to render harmless or to remove any harmful agent that may still be present in the body. If portions of tissue have been destroyed, the healing consists essentially in the removal of the changed and dead tissue, and its replacement by new tissue.*

When from any cause the temperature of the body becomes abnormally low or abnormally high, compensation may be effected in such a way that through the suitable regulation of the heat-production and heat-dispersion the temperature of the body may be brought back to the normal. If through trauma a portion of tissue is destroyed, the organism may repair the defect either through the local production of new tissue (*regeneration*) or by a corresponding increase in other similar tissues (*compensatory hypertrophy*).

If **poisons** enter the body and produce symptoms of intoxication, healing can follow only through the rapid *excretion* of the poison, or its *destruction* or *neutralization* within the body; while at the same time the damaged tissues, under the influence of normal nutrition, again return to their normal state, existing defects being properly compensated.

In **infections** the *healing processes* follow directly upon the *action of the protective forces;* indeed, the action of the latter constitutes the first stage of healing; *the protective and healing processes are in part identical.*

In many infectious diseases the healing influence of protective substances already present in the affected body is supplemented by the **appearance of new substances foreign to the normal organism**, which as **bactericidal substances** and as **antitoxins** antagonize both the infection and the intoxication. The **bactericidal antibodies** are formed by the tissue-cells which through the infection have been placed under altered conditions of life; they spread throughout the tissue-juices, and thus hinder the further extension and multiplication of the bacteria. They are formed particularly in typhoid fever, cholera, and plague, and *show constantly a certain specificity* in that they influence primarily those bacteria through whose vital activities they have arisen. This specificity is, however, not absolute, inasmuch as they can act upon closely related species.

Antitoxins are formed in those infections in which toxins are produced. The action of the toxin takes place in this manner (Ehrlich): the poison molecule combines through a haptophorous side-chain with the haptophorous group of certain cells, while the toxophorous side-chain of the poison exerts its influence in a specific manner upon the affected cells, so that we may regard the *antitoxins* as representing nothing more than an excess of *haptophorous side-chains of the cell-substance sus-*

ceptible to the poison, that are given off into the blood-serum and into the body-juices, and combine the corresponding haptophorous side-chains of the toxin. The haptophorous group of the toxin is thereby prevented from carrying over its toxophorous group to the cells and thereby becoming active.

Toxin and antitoxin combine according to fixed quantitative relations.

Antitoxins are formed against the poison of diphtheria and tetanus, the pyocyaneus poison, ricin, snake-poison, the poison of eel-blood, and certain mushroom poisons.

Since the antitoxins of snake-venom (*Calmette*) and that of the pyocyaneus toxin (*Wassermann*) are more easily destroyed than the poisons themselves, it is possible in a mixture of the two, when the combination has lasted but a short time, to destroy by heating to a certain degree the antitoxin alone, so that the toxin again becomes active.

The virulence of the toxin of diphtheria is weakened with age, through the fact that the toxophorous group in part becomes inactive.

If the favorable course and the healing of an infectious disease depend essentially upon the production of antitoxins, the bacteria concerned may still be preserved and increase in numbers; only the harmful action is averted. After a certain time they also die.

According to investigations by *R. Pfeiffer*, confirmed by *Sobernheim, Dunbar, Loeffler*, and others, there is found in the blood-serum of animals made immune against typhoid-bacilli or cholera-spirilla, or of human individuals suffering or convalescing from typhoid fever and cholera, a **specific bactericidal substance** (*lysogenous substance* of *C. Fraenkel*). The addition of such a serum to a virulent bouillon-culture of these bacteria so changes the latter that the bacteria when inoculated into the peritoneal cavity of an experimental animal rapidly disintegrate into little spherules and are finally dissolved.

Bordet has shown that a fresh human serum is active also in the test-tube outside of the human body. When heated to 56° C. this activity is lost (inactivation) but it may be restored again through the addition of normal serum (reactivation).

According to the investigations of *Gruber, Durham, Pfeiffer, Kolle, Sobernheim, Widal, C. Fraenkel*, and others, the blood-serum of individuals ill, convalescing, or entirely recovered from typhoid or cholera exerts a damaging influence upon typhoid-bacilli or cholera-spirilla respectively; this influence being of such a nature that in bouillon-cultures the bacteria so affected become motionless, clump together, sink to the bottom of the vessel, and are destroyed. When the serum is added to a hanging drop of bouillon-culture, the rapidly moving vibrios at once become motionless and collect in little heaps. *Gruber* believes that this phenomenon is to be explained by a swelling and bursting of the membrane of the bacterial cell, and assumes that this change enables the alexins to destroy the bacteria present in the body. He therefore designates the active substances in the serum as *agglutinins*, and believes that to these may be attributed the chief agency in the healing of infectious diseases and in the production of immunity against the same. *Pfeiffer*, on the contrary, denies the occurrence of any swelling of the cell-membrane, and explains the phenomenon as due to an inhibition of development, and designates the active substances, the nature of which is wholly unknown, as *specific paralysins*. After *Gruber* had demonstrated the peculiar action of the blood-serum of typhoid-fever patients, *Widal* (*Sem. médicale*, Paris, 1896) proposed that this action of the blood-serum on cholera-spirilla and typhoid-bacilli respectively be utilized as a diagnostic aid during the course of an attack of typhoid. Numerous clinical investigations have demonstrated that it is possible, during the course of the attack or for a long time (several months) afterward, to make a diagnosis of typhoid from the action of the blood-serum upon cultures of typhoid bacilli (*Widal's reaction*). (See § 33.)

According to *Kraus*, there is present in the blood of animals artificially immunized against cholera and typhoid fever a body, which, on the addition of such a serum to a clear bacteria-free filtrate of cultures of cholera or typhoid bacilli, produces in the latter a clouding and later a precipitation, thus acting as a **precipitin.** (See § 33.)

The **protective substances** which appear in the blood in the course of infectious diseases are not always formed at the same place; in pneumonia they are said to be produced in the bone-marrow (*Wassermann*); in cholera and typhoid fever in the spleen (*Pfeiffer* and *Marx*); in " Rinderpest " in the liver (*Koch*). They are to be regarded as *specific secretory products* arising in response to specific stimuli.

The **bactericidal immune-bodies** are, according to their physical and chemical properties, to be regarded as *ferments* (they are neither globulins nor albumins). The immune-bodies combined with the bacterial cells during bacteriolysis may be set free after the solution of the bacterial protoplasm, and again become capable of action.

It has often been assumed that the **fever** occurring in infectious diseases is a protective process favoring the destruction of bacteria; and it is not impossible that in *individual* cases it may exert such a favorable influence. Thus, for example, it is conceivable that a parasitic micro-organism, growing well at a temperature of 37–38° C., will not thrive at a temperature of 40–41° C., so that high-fever temperatures may hinder its power of reproduction. The conclusion should not, however, be drawn from this that fever is a useful phenomenon which always favors the counterbalancing of pathological disturbances. Even in those cases in which the metabolic processes occurring during the fever exert an injurious influence upon the bacteria, this is not to be taken as proving the usefulness of fever. We can only say that a part of the morbid processes occurring during an infectious fever leads to a formation of decomposition-products which may possess antibacterial or antitoxic properties.

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See also § 30, § 32, and § 33.

II. The Acquiring of Immunity against Infection and Intoxication. Protection through Inoculation.

§ 32. The **acquiring of immunity against a particular infectious disease** is a phenomenon whose frequent occurrence has long been known through clinical observations. This fact has been established chiefly by the observation that the great majority of men suffer but one attack of such widespread infections as measles, smallpox, whooping-cough, scarlet fever, and diphtheria, and that after such attack they are spared by the disease, even when they expose themselves under the most varied conditions to the danger of infection with its poison. The knowledge of this fact is very old, and early in the eighteenth century it had led, in the Orient, to attempts to obtain immunity against the natural contagion of smallpox by the inoculation of material from smallpox pustules. In the latter part of the eighteenth century Jenner discovered that the disease known as cowpox—i.e., a milder form of pox, which is an attenuated form of human smallpox—afforded protection against the true smallpox. As a result of this observation, since the beginning of the year 1796, at first by Jenner himself, afterward by the physicians of all civilized countries, artificial inoculations of cowpox have been carried out upon millions of human individuals, with the result that through such inoculation a high degree of immunity against the true smallpox has been secured to the inoculated; so that at the present time, in all countries where vaccination is universally practised, the occurrence of widespread epidemics of smallpox, once so frequent, is very rare, and the disease no longer assumes the character of a dangerous pestilence.

The investigations of the last decades with regard to the causes and origin of infectious diseases, which have covered such an extraordinarily broad field, have shown that the **acquiring of immunity against a certain infectious disease through one attack of the given disease** occurs in different infectious diseases, especially in those running an acute course; and represents sometimes a transitory, at other times a permanent peculiarity of the individual concerned, which in pregnant women may be transmitted to the fœtus *in utero*. These observations have also shown that the single or repeated **inoculation of attenuated pathogenic bacteria**—that is, of bacteria which on account of their slight virulence produce a disease that, in contrast to the natural infection with bacteria of full virulence, is relatively insignificant, often localized to a limited area—can also confer immunity against the corresponding disease. Further, it has been demonstrated that the **injection of certain**

chemical substances produced by the bacteria is sufficient to confer immunity against certain infections.

Immunity through the inoculation of attenuated specific disease-germs may be produced, for example, against anthrax, symptomatic anthrax, chicken-cholera, diphtheria, and swine-erysipelas. The weakening of the virulence of bacteria may be produced either by the action of high temperatures or chemical agents, or by the action of the air alone; further, it may also be produced by the inoculation of the bacteria into certain animals or through their long-continued cultivation on artificial media. Inoculation is, in general, carried out by injecting subcutaneously first markedly attenuated, then less attenuated, and finally fully virulent bacteria together with their products.

According to the investigations of numerous authors, immunity in animals may also be produced by the **injection of sterilized cultures** in which the bacteria are completely killed—as, for example, against American hog-cholera, symptomatic anthrax, diphtheria, the infectious disease produced experimentally in rabbits by the injection of the *Bacillus pyocyaneus*, and the infection produced in guinea-pigs by cholera-spirilla.

A third form of artificial immunization, which Raynaud attempted as early as 1877, but was first securely established by Behring in 1890, can be produced by the injection into man or an experimental animal of **blood-serum taken from animals which were previously susceptible, but have been rendered immune by means of inoculations.** The most extensive and at the same time the most successful attempts thus far made have been carried out with *diphtheria* and *tetanus;* that is, in diseases in which intoxication through toxins forms the most striking feature. Moreover, successful experiments with the blood-serum of immunized animals, in the case of cholera, swine-erysipleas, anthrax, typhoid fever, and plague, have been reported.

The specific protection which the blood-serum affords may be secured, not only by injection before infection occurs, but also after infection has already taken place; so that the serum may be designated not only a **protective serum**, but also a **healing serum.** For both protection against and for the cure of a certain infection a *definite amount of serum* is necessary, the precise amount depending, on one hand, upon the severity of the infection, and on the other, upon the activity of the serum itself, which increases with the completeness of the immunization of the originally susceptible animal furnishing the serum. If the serum is not injected until after infection has occurred, the amount of serum must be so much the greater the longer the lapse of time after the beginning of the infection.

In the case of true bacillary *diphtheria*, the injection of curative diphtheria-serum has now been carried out in thousands of cases, of both severe and light forms; and there is without any doubt a beneficial influence exerted upon the course of the disease, as shown by a rapid improvement of the patient's general condition (rapid establishment of euphoria, fall of fever, improvement in the pulse), as well as by the favorable course pursued by the local disease. In *tetanus* a definite curative action of serum has been demonstrated in the case of experimental animals, guinea-pigs, and mice; but the results in man have not yet been fully determined.

The blood-serum of immunized animals exerts its beneficial action, without doubt, through the presence of a *counter-poison*, an **antitoxin**, which neutralizes the poisons produced by the bacteria. In the case of

the patients treated by a given antitoxin, there is produced a **poison-immunity** against the corresponding bacterial poison—as, for example, against the poison produced by the diphtheria-bacilli, in those patients injected with diphtheria-antitoxin—and this immunity is to be ascribed to the presence of a definite amount of antitoxin in the blood.

Besides the antitoxins, the blood-serum of immunized animals or human beings may also contain **bactericidal substances**, which injure or kill the bacteria themselves; and this is said to occur especially in cholera and typhoid infections.

In the case of immunization by means of attenuated cultures or by sterilized chemical bacterial products, the antibodies are produced as new substances within the organism, and this process has been designated **active immunization** (Ehrlich); in the case of the injection of immunizing serum the antitoxin already formed is introduced from without, and this may be spoken of as **passive immunization**. It is probable that in the last case no new-formation of antitoxin occurs after the injection.

For the foundation researches in regard to inoculation with attenuated cultures of bacilli cultivated outside of the body, we are indebted to *Pasteur*, who, in 1880, demonstrated the fact that chickens could be immunized against chicken-cholera through the inoculation of cultures of *chicken-cholera bacilli*, that had been weakened through long exposure to the air.

Since that time numerous experiments have been carried out with other forms of bacteria, especially with attenuated cultures of the bacilli of anthrax and symptomatic anthrax. Good results have been obtained from inoculations against the symptomatic anthrax of cattle. Less favorable are the results in inoculations against anthrax, in that some of the animals die from the effects of the protective inoculation, while others are not rendered absolutely immune against a new anthrax infection.

Sheep and cattle may be made immune against *anthrax*; most expediently (*Koch*) by first inoculating them with attenuated cultures of anthrax-bacilli, which will kill mice but not guinea-pigs, and then with those which will kill guinea-pigs but not large rabbits.

As vaccine against *symptomatic anthrax*, there may be used cultures of the bacillus attenuated through heat or such chemical agents as sublimate solutions, thymol, eucalyptol, and silver nitrate; and by such inoculations cattle may be rendered immune. At the present time heat (*Hess, Kitt*) is most commonly used in the preparation of the vaccine. The infected muscle of an animal dying with symptomatic anthrax is chopped fine, triturated with one-half its weight of water, and pressed through a piece of linen cloth. Finally, the fluid is again filtered through a moistened piece of fine linen. The virulent material is then spread in thin layers upon glass plates or flat dishes, and transferred to a dry chamber at a temperature of 32–35° C. When thoroughly dry the virus is scraped off and removed in the form of powder. When it is desired to give inoculations, the virus is triturated with double its weight of water and the fluid evaporated in a thermostat. By raising the temperature to 100° C. for six hours a weak vaccine is obtained; at a temperature of 85° C. for six hours a stronger one. For the immunization of cattle, about 0.5 gm. of the weaker virus in a dilute water solution is injected into the subcutaneous tissue of the animal's tail, and after eight to twelve days the stronger solution is similarly injected.

According to observations of *Chauveau* and others, protective inoculations may also be made by the injection of virulent bacteria in very small quantities, or in such a manner that the life of the animal shall not be endangered. In the case of symptomatic anthrax this may be accomplished by the injection of very small doses into the extremity of the animal's tail; such injections not causing a fatal illness, but only a local disturbance.

According to *Afanassieff*, it is possible to render animals immune by inoculating the granulating surface of a wound with a virulent culture.

Cattle may also be immunized against *contagious pleuropneumonia* (*Schütz*) by injecting the tissue-juices from the lung of an animal dying from this disease into the tip of the tail. There is produced in this way a circumscribed inflammation, or, at least, one which is confined to the tail; after recovery from which the animal is immune to both natural and artificial infection with this disease.

Hogs may be rendered immune against inoculation with virulent bacilli of *swine-*

erysipelas (*Pasteur*), by using, as vaccine, cultures attenuated by successive inoculations in rabbits. According to *Emmerich*, rabbits may also be made immune against the bacilli of swine-erysipelas through the injection into the ear-vein of a small quantity of a virulent bouillon-culture diluted with fifty times its volume of water.

Animals susceptible to *diphtheria* may be rendered *immune* against this disease, according to *Behring*, by the injection of cultures of diphtheria-bacilli which have been weakened in virulence by exposure for sixteen hours to iodine trichloride (1:500). Two cubic centimetres of such a culture are injected into the peritoneal cavity; after three weeks this injection is repeated with a diphtheria-culture (0.2 c.c.) which has been washed four days in bouillon containing iodine trichloride (1:5,500). After this, fully-virulent cultures are injected in increasing doses.

Protective inoculations against *rabies* were first carried out in cases resulting from bites by rabid animals, particularly in France (Pasteur Institute), Russia, and Italy. As inoculation-material, the spinal cord from rabbits which have been infected with rabies is used after it has been dried in dry air at a temperature of 23–25° C.; the virulency of the cord being gradually lost after about fifteen days of the drying-process. According to *Protopopoff*, it is the temperature, and not the drying (*Pasteur*), which lessens the virulence. According to *Marx*, the micro-organisms of rabies have already been weakened in the body of the rabbit. Small portions of a rabbit's cord thus weakened in virulence are triturated in sterilized chicken-broth and injected subcutaneously into the bitten individual; at first pieces of cord greatly reduced in virulence are used, then those of gradually increasing virulence. According to the view held by *Pasteur*, the spinal cord contains both the microbes of the disease and the specific poison formed by them; if the latter spreads through the body more rapidly than the microbes, it confers an immunity against a subsequent spread of the microbes, and affords protection to the nervous system in particular. In order to confer immunity it is, therefore, necessary to introduce as large a quantity as possible of the chemical poison. According to the reports of the Institutes in which the Pasteur inoculations against hydrophobia have been carried out, it must be acknowledged that these inoculations have been successful in preventing cases of hydrophobia.

Immunity against *cholera* may be produced, in both man and animals (*Haffkine*, *Pfeiffer*, *Kolle*, *Voges*, and others), by the injection of sterilized or attenuated cultures of cholera-spirilla; this immunity (which is of short duration) depends upon the formation of *specific bactericidal anti-bodies* in the blood (see Voges, l. c.). On the other hand, we do not yet possess a specific remedy by which the life of any animal or man infected with cholera may be saved.

Immunity against *typhoid fever* may be secured in man by the subcutaneous injection of sterilized cultures of typhoid-bacilli (*Pfeiffer*, *Kolle*); and the establishment of the immunity may be recognized by the fact that the blood-serum of the individual so inoculated is found, after a few days, to contain *bactericidal substances*. Attempts at immunization in cases already ill with typhoid (*Brieger*, *Wassermann*, *C. Fraenkel*) have up to the present time been unsuccessful.

According to the reports published by *Koch* (*British Medical Journal*, 1897; *Deut. med. Wochen.*, 1897, No. 16; *Centralbatt f. Bakt.*, xxi., p. 526) of the investigations which were carried out during the winter of 1896–1897 with regard to the cattle-plague in Cape Colony, cattle may be immunized against "*Rinderpest*" by subcutaneous injections of 10 c.c. of the bile taken from animals dying of the disease; the condition of immunity becoming established at the latest by the tenth day. According to the report of Professor Winkler ("Landwirthschaftl. Bezirks-Verein Giessen," August, 1900) hogs and cattle may be immunized against *foot-and-mouth disease* through feeding with milk of animals which are affected by the disease or have recently recovered from it. *Loeffler* and *Uhlenhuth* (*Contralblatt f. Bakt.*, xxix., 1901) have also reported successful protective inoculations with a serum against the foot-and-mouth disease.

In the year 1890 *Koch* made the discovery that cultures of tubercle-bacilli contain an active substance, "*tuberculin*," which, when injected into tuberculous individuals, causes a rise of temperature and to some extent local inflammatory changes in the neighborhood of tuberculous foci. It was at first hoped that in tuberculin a remedy for tuberculosis had been found, but the many trials made with it upon human beings and animals have shown that it indeed produces after repeated injections an immunity against the toxic action of tuberculin, but does not hinder the multiplication of tubercle-bacilli and the consequent spread of the disease. Further, the local inflammation caused by the tuberculin leads to favorable results only under special conditions, but, on the other hand, often causes actual harm (through the metastasis of bacilli). Nevertheless, Koch's discovery has proved of great importance. In the first place, it is of practical value in the diagnosis of tuberculosis, in that tuberculin injections do not excite fever in normal individuals. Inoculations for diagnostic purposes are now used very extensively in cases of suspected tuberculosis in domestic animals. Moreover, the reports published by *Koch* gave a great stimulus to further investigations with re-

gard to immunization by means of inoculation with bacterial toxins; and these investigations have led to the discovery of the antibodies of diphtheria, tetanus, cholera, and typhoid fever. Small doses of tuberculin appear also to have a favorable influence upon the course of tuberculosis.

In 1897 *Koch* ("Ueber neue Tuberculinpräparate," *Deut. med. Woch.*, 1897) succeeded in obtaining from highly virulent cultures of tubercle-bacilli a substance which he claims is able to immunize against all of the constituents of the tubercle-bacillus. To obtain this substance young cultures of tubercle-bacilli are dried in a vacuum-exsiccator and then triturated. The product obtained by trituration is mixed with distilled water and centrifugated. The active substance is contained in the muddy precipitate thus obtained (designated by *Koch* as T. R.). This is again dried and triturated, dissolved in water to which twenty per cent of glycerin is added for the purpose of preservation. (The preparation is manufactured by *Meister, Lucius*, and *Brünning*, at Höchst-on-the-Main, Germany.) The fluid preparation contains 10 mgm. of solid substance in every cubic centimetre, and when it is to be used should be diluted with physiological salt solution. Through the use of large doses animals are said to become immunized in from two to three weeks. In the treatment of tuberculosis in man the dose should begin at $\frac{1}{500}$ mgm. and gradually be increased up to 20 mgm., the injections being given every other day. According to the observations so far published, the T. R. preparation does not appear to exert a curative action upon tuberculosis in man.

The **blood-serum treatment of diphtheria,** i.e., the employment of the antitoxins contained in the blood of an animal immunized against diphtheria as a means of curing that disease when it is already contracted, or as a protection against such infection, is a discovery which we owe to *Behring*. The favorable effects of the method discovered and proved by him through experimental investigations have been confirmed by thousands of observations. In the treatment of diphtheria patients a large quantity of the serum (one thousand immunizing units) is usually injected at one time beneath the skin of the thigh.

The term "normal serum"—i.e., a serum having the value of one immunization unit—is used by *Behring* to designate a serum which, when mixed with a quantity of diphtheria poison equal to ten times the minimal fatal dose and then injected in the amount of 0.1 c.c. into a guinea-pig of from 200 to 300 gm. weight, will surely protect that animal from diphtheria. Sheep and horses are especially adapted for the preparation of the serum. It is prepared and sold in doses of from five hundred to three thousand immunization units.

If culture-filtrates of the **tetanus-bacillus** are weakened by the action of chemical agents (iodine trichloride or iodine combined with potassium iodide), it is possible through repeated injections of such filtrates of increasing virulence to produce immunity in animals against tetanus (*Kitasato, Behring, Tizzoni, Buchner*). The blood of such immunized animals contains an *antitoxin which affords a sure protection to experimental animals against tetanus.* The antitoxin treatment of human beings suffering from tetanus has not given satisfactory results (see *Kohler* and *Schlesinger*, l.c.), not even in cases of relatively early injection of the antitoxin, though it appears to be effective if administered before the appearance of the tetanus.

Susceptible animals and human beings may be immunized against *bubonic plague* by means of sterilized cultures of the pest-bacillus (*Yersin, Haffkine, Kolle*); and it appears that in the blood-serum of immunized animals (the horse, for example) there are present anti-bodies which render the serum utilizable for both protective and curative purposes.

Animals may be made immune against *snake-poisons* by means of inoculations of very small doses of such poison continued for some length of time (*Calmette, Tschistowitsch*); and the blood-serum of such immunized animals is also found to possess an antitoxic action against the given poison, so that it may be used as a healing-serum. In Brazil, Mexico, Africa, etc., various methods involving the use of snake-poison itself are employed for the immunization of individuals against a snake-bite, or for curing them after they have been bitten (drinking of the secretions of the poison-glands, rubbing of the diluted poison into small wounds of the skin, etc.) (*Brenning*).

According to the investigations by *Ehrlich*, mice may be made immune against *ricin*, to which they are extremely susceptible, by mixing very small doses of ricin with their food and then afterward injecting additional small doses subcutaneously. The appearance of the immunity occurs on the sixth day after the administration of the ricin, so that upon this day the animal can withstand a dose thirteen times as great as at the beginning. Through continued systematic inoculations the animal becomes immune to a dose eight hundredfold as strong. The immunity is produced by an antitoxic body, antiricin, which neutralizes the poisonous action of ricin.

Vaccines. Since Wright's discovery of the opsonins, *bacterial vaccines* have been extensively employed in the treatment of certain infections. The vaccines are prepared by cultivating the given organism on agar-agar, suspending the growth in salt-solu-

tion, and heating to 65°–80° C. for an hour to kill the bacteria. The emulsion of dead bacteria is then injected. Immediately following the injection the opsonic index falls for a time, the so-called negative phase. This is followed in a day or two by a rise in the index to or above its original height, the positive phase. Considerable doubt has been thrown upon the opsonic index as a reliable guide in the progress of an infection; but many clinicians have obtained gratifying results in the treatment with bacterial vaccines. The conditions most amenable to this treatment are localized inflammations caused by staphylococci, streptococci, pneumococci, gonococci, and the tubercle-bacillus. As the method of treatment is still in the experimental stage, it is too early to make definite statements concerning its value.

Attempts have been made to treat thyroidism with a specific serum (*Rogers, Beebe*). Experimental immunity to *Spirillum obermeieri* can be produced by the injection of filtered blood in which the spirilla have died out (*Novy*). Experimental immunity can be obtained in experimental cerebrospinal meningitis (*Flexner*).

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See also §§ 30, 31, and 33.

III. The Active Substances of Acquired Immunity. Ehrlich's Side-chain Theory.

§ 33. **Acquired Immunity** depends upon the presence of **specific antitoxic and bactericidal antibodies.** The process is seen in its simplest form in the production of antitoxins, a phenomenon most familiar to us in the healing of diphtheria and tetanus.

According to the views of Ehrlich, only those substances are **poisons** that possess a chemical affinity for some element of the body and through a combination with this exert a harmful action recognizable clinically. A congenital **immunity to poison** may, therefore, depend upon the fact that the poison finds in the immune-body no element with which it can react chemically, or the element so affected suffers no damage in a clinical sense. In **acquired immunity to poison** the **poisonous action of the toxin is prevented through the formation of an antitoxin.**

The complex **protoplasmic substances,** when considered as chemical structures, consist of (Ehrlich) a *governing-nucleus* or *central-group* (*central ring*) and of various *side-chains.* These side-chains can combine with the side-chains of albuminous *nutritive* substances, and so bring about an assimilation of the latter. They thus have the significance of *receptors*

or of a *haptophore group* which combines with a *haptophorous group* of the albuminous food-material. In the same way **toxins** *are anchored through their haptophorous group to the receptors of the cell-protoplasm, thus enabling the toxophorous group of the toxin to exert its action upon the cell-protoplasm and to injure the vital powers of the cells.*

As the result of the combination of the toxins with the receptors, portions of the protoplasmic albumin-molecule are rendered incapable of functionating. If the life of the cell and its power of compensation are not damaged, there is produced only a functional disturbance of the central-group without any definite injury to it; and the cell may again replace the side-chains and even form them in excess, throw them off, and give them to the blood. *Such detached side-chains or receptors constitute an* **antitoxin.** The *antitoxin* is, therefore, no new substance, but one normally present, which under certain conditions is produced in an increased amount and given off into the blood, and, circulating there, *combines the toxin present in the blood to form a harmless body, and so prevent its action upon the cells.* The same substance in the living body, which as a constituent of the cells renders intoxication possible, becomes the cause of healing when set free into the blood-stream (von Behring).

The **bactericidal action of the blood-serum,** a phenomenon occurring in certain infectious diseases (typhoid fever, cholera, plague), is dependent upon the *combined action of two substances.* One of these is a *ferment-like body* found in the tissue-juices, and particularly in the blood-serum of the normal organism. It is very labile and is destroyed by heating to 55° C. Buchner has designated this substance as **alexin,** Ehrlich as **complement** (earlier as *addiment*), and Metschnikoff as *cytase.* It alone is not able to injure the bacteria, but needs for this action the coöperation of an **intermediate-body,** the **amboceptor** or **immune-body** of Ehrlich (substance sensibilatrice of Bordet).

The amboceptors are occasionally formed first during the course of an infection, and are specific for that infectious disease (specific immune-bodies), that is, they are active only in that disease in the course of which they are formed. They possess two haptophore groups, one of which (cytophile group) combines with a receptor of the bacterial protoplasm; the other (complementophile group) combines with a haptophore chain of the complement, so that the zymotic group of the latter can act upon the bacterial cells. The amboceptor is less susceptible to heat than the complement and is not destroyed by heating to 60° C.

The **bactericidal sera** act, in the first place, in such a way as to cause the **death and solution of the bacteria,** in that the *specific immune-body,* the amboceptor, carries over to the bacteria the digestive action of the normal body-juices, in the complement, so that the bacteria are in part dissolved. Such sera contain, therefore, **bacteriolysins.** A second action is shown by them in the phenomenon of **agglutination,** in that specific substances contained in the serum, the **agglutinins,** combine with the bacterial cells and cause a characteristic clumping of the bacteria contained in a uniform suspension. The agglutinins are less susceptible to heat than are the lysins and are not changed at 56° C.

Finally, bactericidal immune-sera cause also the phenomenon of precipitation, in that certain substances contained in the same, **precipitins,** or **coagulins,** form chemical combinations with certain substances given off from the disintegrating bacterial bodies and coagulate or precipitate them. If an active bactericidal serum be added to a clear fluid which contains such albuminous substances of the bacterial cells, there is quickly produced a flocculent precipitate.

Precipitins withstand heating to 56° C. and may be dried without losing their potency.

According to Ehrlich, the receptors for a toxin represent only a haptophorous group of the cells with whose haptophorous chain the toxin has combined. He designates the same as a *receptor of the I order.* On the other hand, the receptor of the cells for the nutritive albumin-molecules contains a haptophorous and a zymophorous group, the latter of which causes a fermentative disintegration of the anchored albumin-molecule. This is designated as a *receptor of the II order.* The receptor for bacteriolysin contains a haptophorous group for the anchoring of the ferment-like complement and a receptor for the combining of the disintegration products of bacteria, so that the former can act upon the latter.

The receptors thrown off by the cells are designated by Ehrlich as **haptins,** and he distinguishes: a *haptin of the I order,* the antitoxin, which combines the toxin to form a harmless body; *haptins of the II order,* the agglutinins, precipitins, or coagulins, which, after their union with the albumin of the bacteria, cause agglutination, coagulation, and precipitation through the action of the zymophorous group; and *haptins of the III order,* or bacteriolysins, which as amboceptors carry over the fermentative action of the complement to the bacteria.

Under especial conditions there appear in the tissue-juices, particularly in the blood, substances that act upon the red blood-cells or tissue-cells or the soluble albumins of the human and animal organism in the same manner as the antibodies described above. According to their action they are classed as **hæmolysins** (globulicidal immune-sera), **cytolysins, precipitins,** and **agglutinins.** They arise when into the body of an animal there is introduced the blood, lymph, milk, or tissue from an animal of a different species (*Bordet, Tschistowitsch, Kraus, von Dungern, Wassermann, Ehrlich, Morgenroth, Landsteiner, Uhlenhuth,* and others). The blood-serum of a guinea-pig injected repeatedly with defibrinated rabbit's blood is able to dissolve quickly *in vitro* the red corpuscles of the rabbit, while normal guinea-pig's blood does not possess such a power.

The action of **hæmolysins** or of a *globulicidal immune-serum* corresponds in all respects to that of the bacteriolysins, and the researches concerning the nature of the hæmolysins (*Ehrlich, Morgenroth*) have aided essentially in the explanation of the mechanism of the process of bacteriolysis.

The immune-body or amboceptor appearing in globulicidal serum shows a great specific affinity for the corresponding erythrocytes; it will combine with them at 0° C. and, when thus separated from the complement left in the serum, is not in itself able to dissolve the red blood-cells. The complement will not combine with the red cells without the immune-body. When the immune-body or amboceptor is present, the complement may, at a higher temperature, be carried by the amboceptor over to the red cells and cause their solution.

After intraperitoneal injections of laked blood of the same species, the so-called *isolysins* may be formed, that is, the blood-serum of the animal injected acquires the power of dissolving the red cells of another individual of the same species.

Cytolysins or *cytotoxins* arise through the injection of foreign cells into an organism, for example, after the injection of ciliated epithelium, spermatozoa, leucocytes, renal epithelium, adrenal cells, brain-substance, pancreas-cells, placenta-cells, and carcinoma-cells. In the case of ciliated epithelial cells and spermatozoa the action of the cytolysins contained in the serum can be recognized outside of the body in the rapid cessation of movement (tricholysin, spermolysin).

Cytolysins act in the same manner as the hæmolysins.

Precipitins arise in the blood-serum as a specific reaction of the body after the subcutaneous, intraperitoneal, or intravenous introduction of foreign albuminous substances.

A serum containing precipitins has the power, when added to the albumin solution used in the injections, of causing in the latter a precipitate. *R. Kraus* has demonstrated this action first for cholera-spirilla, that is, for the substance of the bacterial cell brought into solution. The serum of goats previously treated with injections of cholera-spirilla or with the bacterial substance causes a precipitate in filtrates of cholera-cultures that contain no bacilli. This property of the bacterial precipitins may be used in diagnosis.

According to the investigations of *Tschistowitsch, Bordet, Wassermann, Schütze,*

Ehrlich, Morgenroth, Myers, Uhlenhuth, von Dungern, and others, such precipitins are also formed after the injection of foreign blood, milk, inflammatory exudates, fresh and dried flesh, etc.; and through the aid of this method it becomes possible to distinguish from one another not only the red blood-cells of different species, but also flesh, milk, semen, etc.; that is, the precipitating serum of an animal A, that has been treated with an albumin of an animal B of another species, will precipitate the albumin of B, but not that of a third species.

This reaction of albumin obtained by biological methods (*biological method of differentiating albumins*, Wassermann and Schütze) is so extremely sensitive that the specific test for albumin is possible even at a dilution of 1:100,000. The precipitin reaction has found its most important application in the examination of *blood-stains*, but it is also of use in the differentiation of different kinds of meat, milk, etc., and can be applied also to the differentiation of plant-albumins.

The reaction is specific for the albumin of different species of animals and for man; between the albumins of different elements of the body, as, for example, between chicken-blood and the white of a chicken-egg, there exist only quantitative differences. An antiserum to human blood will precipitate also urine containing albumin, purulent exudates, ascitic fluid, seminal fluid, etc.; so it may be inferred that the various fluids of the body contain the same receptors as those of the blood-serum. In the examination of spots, stains, etc., the first thing to be determined is the presence of blood (guaiacum test, Teichmann's test, spectroscopic examination). When this is determined, the biological test, properly handled, gives very certain results, particularly when the animal used for the production of the serum is not closely related. An antiserum for human blood gives only a very weak reaction with ape's blood (particularly that of anthropoid apes); and similar conditions exist between the horse and the donkey, and between the chicken and pigeon.

For the demonstration of the presence of human blood or albumin, the serum of rabbits properly treated beforehand can be used to best advantage, but that of the horse, sheep, or goat may also be employed (according to *von Dungern*, cold-blooded animals produce no precipitins). To produce the antiserum (*Uhlenhuth*) 5–10 c.c. of a dilute solution of albumin derived from human tissues or blood are injected into a rabbit at intervals of several days, until a test of blood taken from the vein of the ear, made about five days after the last injection, shows the serum to be active. It is very strange that the time in which this change in the serum occurs varies greatly with individual animals. When the serum has attained its full strength, the animal is anæsthetized, the thorax opened, and a cut made into the heart. The blood flowing into the thoracic cavity is taken up by a pipette and collected in a sterilized glass graduate. The serum when separated is filtered through a Berkefeld filter and when ready for use must be perfectly clear. The albuminous material to be tested is dissolved in physiological salt-solution.

A serum of high potency may contain precipitins that act not only upon homologous albumins, but also upon heterologous. *Uhlenhuth* recommends, therefore, a marked dilution (1:1,000) of the fluid to be examined, which, moreover, must be perfectly clear. To 2.0 c.c. of the dilute fluid 0.1 c.c. of the antiserum is added, and in the presence of homologous albumin a cloudy precipitate forms at once or after one or two minutes.

Agglutinins that cause clumping through their functional molecule-groups may be combined first with bacteria, but also after that with red blood-cells. Agglutinable substances and agglutinins possess specific combining haptophore-groups (*Eisenberg* and *Volk, Wassermann*). In the agglutinable substance the functional group is more labile and more easily destroyed than the haptophore-group; this is true also of the agglutinin (*Wassermann*). Through external influences the functional group may be lost, and from the agglutinin there is produced an agglutinoid, which is no longer able to cause agglutination, and through its combination with the agglutinable substance is able to prevent the occurrence of agglutination in the presence of agglutinin. As has been mentioned above (§ 31), agglutination has been observed chiefly in the case of cholera-spirilla, typhoid-bacilli, pyocyaneus, colon, and tubercle bacilli.

Immune-agglutinins are produced during the process of immunization by an increased formation and setting free of groups that under certain conditions occur in slight amount even in normal serum.

Agglutination can be applied to the diagnosis of the given disease, but it must be remembered that the serum of healthy individuals causes agglutination (in typhoid fever even in dilutions of 1:20, while the serum of persons having the disease will agglutinate at a dilution of 1:50); and that a serum can also agglutinate to a greater or less degree other bacteria than the one coming under the influence of its agglutination power. The serum of typhoid patients or of those immune to typhoid acts upon many colon-species even in high dilutions.

The precipitable substance in culture-fluids is, according to Wassermann, identical

with the agglutinable substance in the bacterial cells; that is, the substance present in the uninjured bacterial cells, combining in agglutination with the agglutinating serum, is, in the culture-fluids, dissolved out of the bacteria, set free in the same, and gives there a specific precipitate with the serum.

Agglutination and dissolution of the bacteria, according to *Wassermann*, *Ehrlich*, *Morgenroth*, etc., are not caused by the same substance, as is believed by *von Baumgarten* and *Gruber* to be the case. Agglutinins and amboceptors or immune-bodies are two bodies distinct from each other and do not have the same haptophorous group in common. The immune-body needs for its action the complement, the agglutinin does not.

The agglutinin is made up of separate or partial agglutinins, and a bacterial agglutinin may, therefore, vary in its constitution according to the biological qualities of the animal in which it is produced. Two varieties of bacteria (typhoid-fever and colon-bacilli) may also possess a number of partial agglutinins in common. It, therefore, becomes necessary (*Wassermann*), when applying agglutination-tests for the purpose of diagnosis, to work always with such dilutions as possess a limit of action not far from that obtained by titration for the given bacterial species (the limits of potency of any serum may vary greatly). A positive agglutination is, therefore, decisive as pertaining to that species with which the animal producing the serum was previously treated.

The **production of antitoxin** plays the most important rôle in the healing of diphtheria and tetanus; the success attending the prophylactic and therapeutic use of these antitoxins has already been mentioned in § 32. Antitoxins are also produced in the course of infections with the staphylococcus, streptococcus, pneumococcus, intoxications due to Bac. botulinus (sausage-poisoning) and the Bac. pyocyaneus, but the results of the therapeutic applications of these are at the present time uncertain.

Antitoxins are also produced in poisoning with ricin, abrin, crotin, pollen-toxin, mushroom-poison, snake-venom, eel-poison, and the poison of toads and spiders.

The toxin is not destroyed by the antitoxin. When snake-venom (*Calmette*) is mixed with antitoxin so that the mixture becomes harmless to animals, and if the more thermolabile antitoxin be destroyed by heating to 68° C., the mixture again becomes poisonous. The same thing may be demonstrated in the case of the toxin and antitoxin of the Bac. pyocyaneus.

According to *Wassermann*, the substance of the central nervous system chiefly affected by tetanus is able to combine with the tetanus toxin after the manner of an antitoxin and so render it harmless. Tetanus toxin rubbed up with the brain substance of a normal rabbit becomes so weakened that guinea-pigs can bear ten times the fatal dose without damage. According to *Ransom*, the tetanus-poison injected in fatal doses into pigeons is demonstrable in all organs except the central nervous system, with which it has entered into chemical combination.

Therapeutic attempts with **bactericidal sera** have up to the present time not given such good results as those of antitoxic sera. In the first place, the bactericidal sera have no influence upon an existing intoxication. Further, an action upon the bacteria present is also impossible when the injected serum finds no free complement in the blood of the patient or when the amboceptor from animal blood (horse blood) does not combine with the complement of human blood.

The agglutinins, precipitins, etc., can in turn produce in the organism anti-antibodies, antiagglutinins, antiprecipitins, etc.

Hypersusceptibility or **anaphylaxis.** Animals may react to certain toxic or foreign substances in one of two ways, either by an increased resistance or immunity or by an increased susceptibility (hypersusceptibility or anaphylaxis). According to *Theobald Smith*, *Otto*, *Rosenau* and *Anderson*, *Gay* and *Southard*, etc., there occurs a remarkable toxic action in guinea-pigs as the result of an injection of a small dose of horse-serum (.0001-.1 c.c), followed after ten days or two weeks by a second injection of relatively large amount (5 c.c), the reaction being characterized by severe symptoms with death within one hour. This reaction is specific in that guinea-pigs sensitized with horse-serum do not react to the second injection of other proteid substances, and *vice versa*. The reaction following a second injection of the same proteid in guinea-pigs appears to be common to all higher forms of albuminous substances (white of egg. hæmoglobin, milk, extract of peas, bacterial proteids, etc.). Simpler albuminous substances, such as peptone, seem to have slight sensitizing and poisonous properties, while lower nitrogenous compounds as leucin and tyrosin possess none at all. Hypersusceptibility in the guinea-pig may be transmitted by the female to the offspring. The hypersusceptibility may persist for a long time (*Rosenau* and *Anderson*). The hypersusceptibility produced in guinea-pigs to second injections of bacterial proteids resembles that produced by second injections of horse-serum. It is significant that the period of incubation in a number of infectious diseases corresponds to the ten to fourteen days required to sensitize animals to a foreign proteid. (For literature see *Anderson* and *Rosenau*, *Jour. of Med. Res.*, July, 1908.)

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CHAPTER IV.

Disturbances in the Circulation of the Blood and of the Lymph.

I. General Disturbances of the Circulation Dependent upon Changes in the Function of the Heart, Changes in the General Vascular Resistance and Changes in the Mass of the Blood.

§ 34. The mass of blood is kept constantly in motion by means of the rhythmical contractions of the auricles and ventricles of the heart. The blood, as it is driven into the elastic tube of the aorta toward the periphery of the body, meets a significant degree of resistance, which is caused by the friction in the innumerable divisions and subdivisions of the arterial system. This resistance occasions a relatively high pressure throughout the entire arterial system, which in the human femoral artery equals that of about 120 mm. of mercury. After passing through the capillaries the blood arrives in the veins with very little velocity, and stands in the veins under a very slight pressure, which varies according to the location of the vein, and is greatest where a high column of blood rests upon the lumen of the vein. In the great venous trunks in the neighborhood of the thorax the pressure is usually negative, especially during inspiration, as the thorax during this stage of respiration aspirates the blood from the veins lying outside of the chest. Only during forced expiration does the positive pressure in the veins rise somewhat higher.

Assuming the mass of the blood to be constant, the degree of pressure *within the aorta*, at any given moment, is dependent upon the work of the heart and the resistance in the arterial system. The latter in turn is dependent upon the variations in the total diameter of the combined cross-sections of the blood-vessels, due to the elasticity and contractility of the arteries. In the major circulation the arterial tone is very pronounced; in the lesser circulation it is slight, the blood-pressure in the pulmonary artery being only from one-third to two-fifths that in the aorta. Both the heart and the arteries are under the influence of the nervous system, which regulates their activity.

The activity of the heart consists in rhythmical contractions of its musculature; and its normal efficiency presupposes that the heart-muscle, and also the cardiac ganglia, are sound. Every disease of the heart, therefore, in so far as it diminishes the contractile capacity of the heart-muscle and lessens the activity of the ganglion-cells, and in so far as a lessened functional activity of certain parts of the cardiac muscle is not compensated by an increased activity of other parts, will **diminish the functional capacity of the heart.**

In many cases in which the functional capacity of the heart-muscle is impaired, certain anatomical changes, such as fatty degeneration and necrosis of its cells, can be demonstrated; in other cases no anatomical

changes can be made out, especially in those cases in which the diminution of working-capacity follows the exhaustion caused by excessive overexertion. This may occur when the heart is forced to work for some time only slightly above the normal, but under unfavorable conditions, as, for example, in cases of elevation of the body-temperature; as well as in cases when for a short period it is overworked to an excessive degree. Under certain conditions disturbances of nutrition and intoxications, such as occur in the infectious fevers, as well as a sudden diminution in blood-supply from the obstruction of a coronary artery, may cause an insufficiency of the heart within so short a time that the heart-muscle presents no recognizable anatomical lesion. The work of the heart may also be made difficult at times through the formation of adhesions between the epicardium and pericardium, and between the latter and the contiguous pleura, in consequence of which the contractions of the heart are hindered.

Through the collection of fluid in the pericardial sac in the course of certain diseases, further, through marked deformities of the thorax causing an abnormal smallness of the thoracic cavity, and through a high position of the diaphragm, the diastolic dilatation of the heart and the free afflux of blood from the veins may be hindered to such an extent that the ventricles receive too little blood. If, following pathological processes in the heart-valves, there result rents or distortions of the flaps or adhesions between them, or if in case of dilatations of the heart and the valvular orifices the valve-flaps become relatively too short, there may arise those conditions of the auricular and ventricular orifices known as insufficiency and stenosis. The former condition is characterized by a failure of a valve to close completely during the diastole of the auricle or ventricle lying behind the given valve; the second condition, by the fact that during the contraction of the auricle or ventricle the valvular orifice does not suffice for the passage of the blood through the opening. The effect of a stenosis is that of opposing additional obstacles to the outflow of the blood during systole. In aortic and pulmonary insufficiency the blood regurgitates, during the ventricular diastole, back from the great vessels into the ventricles; in mitral and tricuspid insufficiency the systole of the ventricle causes a regurgitation into the corresponding auricle.

Finally, there are not infrequently formed in the heart masses of coagula, which under certain conditions—in case they lie near the orifices—may on the one hand interfere with the proper closing of the valves, or on the other cause a narrowing of the ostium.

As the result of all the above-mentioned pathological conditions, the **efficiency of the heart's function is impaired,** so that in a given time too little blood passes into the arterial system, the aortic pressure consequently falls, and the velocity of the blood-current is diminished; while in the venous system the blood collects more and more, and the venous pressure rises. There is consequently an *inadequate filling of the arteries* throughout the entire body, varying, indeed, according to the degree of contraction maintained in individual arterial systems, while both veins and capillaries are, on the other hand, overfilled with blood. There develops, therefore, a condition of general **venous hyperæmia,** which in some parts may become so marked that the tissue, because of the engorgement of the capillaries with venous blood, acquires a *blue-red, cyanotic appearance.* When the difference in pressure between the arterial and venous systems becomes reduced to a certain minimum, the circula-

tion comes to a standstill, while the right side of the heart becomes greatly distended with blood.

Should the contractions of the heart from any cause become weak and imperfect, the pulse-wave also becomes small. If the rate of the heart-beat becomes diminished in frequency, the arterial system empties itself to a greater extent than normally during the pause between the systoles.

If the impairment of cardiac efficiency involves the left heart essentially, as is the case, for instance, in valvular disease of the left side, the disturbance of circulation is manifest first in the systemic arteries, as well as in the pulmonary vessels.

In stenosis of the aortic valves, the arteries, if the heart's action remain unchanged, fill but slowly and incompletely (pulsus tardus). In aortic insufficiency a normal or even an increased amount of blood is thrown into the arteries during systole (pulsus celer), but a part of this flows back again during diastole. In both cases the left ventricle becomes more and more distended, the emptying of the left auricle is hindered, its cavity also becomes dilated, and finally the blood is backed up in the pulmonary veins. Owing, however, to the low pressure in the pulmonary circulation, the blood is readily dammed back upon the right ventricle, and the blood stasis may finally extend beyond this into the right auricle and into the systemic veins.

Valvular lesions at the mitral orifice produce similar effects upon those portions of the circulatory apparatus lying behind the left auricle, as in such cases there is produced also a condition of pulmonary stasis, with a rise of pressure in the pulmonary arteries and veins; while the left ventricle either receives too little blood (stenosis) or during its contraction drives a portion back into the auricle (insufficiency).

In valvular lesions of the orifices of the right heart the damming back of the blood is limited to the veins of the systemic circulation, while in the pulmonary circulation both pressure and velocity are diminished. Further, the pressure in the aorta also falls, since the left side of the heart receives too little blood.

The damming back of the blood in the great systemic veins may manifest itself by *venous pulsations* in the neighborhood of the thorax, inasmuch as retrograde waves of pressure proceeding from the heart may pass through the veins toward the capillaries, distending the veins to such an extent that the venous valves, particularly those of the jugular bulb, are rendered inadequate. The essential condition of the transmission of the venous pulsation is the insufficiency of the venous valves. In the case of imperfect function of the valve in the jugular bulb, a slight pulsation may be observed even during normal action of the heart; but when the veins are distended, and particularly in the case of tricuspid insufficiency, the pulsation becomes much stronger and extends further toward the periphery. If the tricuspid is adequate the venous pulsation (presystolic) is only the expression of the rhythmical occurrence of a hindrance to the outflow of blood from the veins (negative or normal venous pulse). In tricuspid insufficiency the contraction of the right ventricle forces blood back through the tricuspid opening into the right auricle and into the veins beyond, giving rise to a systolic venous pulsation (positive venous pulse).

If in a heart affected with a valvular lesion the chambers lying behind the lesion become distended with blood, the muscular walls of these chambers, in case they are otherwise normal, may by an increased activity **compensate for the valvular lesion** within certain limits. In the

course of time there results an increase in the volume of the heart-muscle, a **hypertrophy of the heart-muscle**, which enables the heart to carry on its increased work for an indefinite period. Such compensation frequently becomes inadequate, with the result that the aortic pressure is permanently lowered, while the venous pressure, on the other hand, is abnormally high. There is, at the same time, the danger that the heart-muscle may in time become exhausted, or that a very slight illness may render the heart insufficient. Thus, for example, a prolonged quickening of the heart's rate, by shortening the diastolic periods of rest, may cause cardiac exhaustion and insufficiency. Arrest of the heart's action finally follows, with great accumulation of blood in the heart, since the heart is no longer able to drive onward the mass of blood entering it.

An **increase of the heart's action**—that is, an increase in the frequency of the heart's contractions, these at the same time remaining strong and complete—causes an increase in arterial pressure and an increased velocity of the blood-current. When increased demands are frequently made upon the left side of the heart—as frequently happens in heavy bodily labor, conditions of luxurious living, abnormal irritability of the cardiac nerves, etc.—the left ventricle may become hypertrophic and act permanently with greater force. Inasmuch as the quickening of the blood-stream causes the right heart to receive a greater amount of blood during diastole, a hypertrophy of the right ventricle is usually found in connection with the hypertrophy of the left ventricle.

Lessening of the mass of blood or **general anæmia** from the loss of blood leads temporarily to a fall of pressure in the aorta; but if the loss of blood was not excessive, the blood-pressure rises again, as the vessels adapt themselves to the changed conditions, and, as the result of the stimulation of the vasomotor centre through local anæmia, show a greater degree of contraction. Under normal conditions the mass of blood is quickly increased through the absorption of fluids, and later by a regeneration of the blood. Similarly, in **anhydræmia**—i.e., a diminution of the water of the blood—the arterial pressure is lowered and the blood-current slowed. After severe hæmorrhages the arterial pressure is lowered for a greater length of time, the circulation is slowed, and the pulse, because of the lessened stimulation of the vagus-centre (Cohnheim), is frequent and small.

In the case of lasting diminution of the blood-mass—i.e., the condition known as **chronic anæmia**, which occurs under varying conditions—the vascular system is imperfectly filled, the blood-pressure lowered, and the blood-current slowed. Both heart and blood-vessels adapt themselves to the new conditions and become diminished in volume. In the case of a marked deficiency of hæmoglobin, degenerations of the heart-muscle, particularly fatty degeneration, frequently occur.

Increase in the mass of the blood, through the injection of blood or salt-solution into the blood-vessels, is followed in animals by only a temporary increase in pressure and in the velocity of the blood-current. A return to the normal is brought about, partly by the dilatation of a part of the vascular system, particularly in the abdomen, and partly through the elimination of the surplus from the vessels. If the mass of blood, as the result of some especial predisposition or of high living, comes to stand in an abnormally high porportion to the body-weight, if there exists a **permanent plethora,** the pressure in the aorta becomes permanently raised, the work of the heart is permanently increased, and there develops a corresponding *hypertrophy of the heart.*

When the arterial blood-pressure is raised there occurs an increased giving-off of fluid from the blood, and thereby a concentration and diminution in the amount of the venous blood; in lowering of the blood-pressure the amount of fluid given off is diminished and eventually an increased taking-up of fluid occurs. This change in the venous blood is under normal conditions compensated for in the lungs: in the first case, through a taking-up of lymph from the lymphatics; in the second case, through a giving-off of lymph to the lymphatics (*Hess:* "Beeinflussung des Flüssigkeitsaustausches zwischen Blut u. Geweben durch Schwankungen des Blutdruckes." *D. Arch. f. klin. Med.*, Bd. 79, 1903).

§ 35. **Increase of the general vascular resistance** may occur in either the greater or the lesser circulation, and results in an increased pressure behind the point of increased resistance, and a diminished pressure beyond it.

In the **systemic circulation** the hindrance may lie either in the main vessel, the aorta, or in the arterial branches, whose degree of contraction maintains and governs the normal pressure in the aorta. Vascular contraction involving a great number of arteries and their branches, and sufficiently well marked to increase the blood-pressure, is generally a temporary phenomenon, passing off with the relaxation of the arterial tension. Nevertheless, a permanent increase in the aortic pressure with consequent hypertrophy of the left ventricle does occur; and this cannot be explained otherwise than as the result of the contraction of the lumen of the smaller arteries. Transitory arterial contraction and increase of pressure occur particularly through an increase of the amount of carbonic acid contained in the blood. A permanent increase of aortic pressure is, on the other hand, a result of chronic diseases of the kidney, in which the secreting parenchyma is destroyed. Inasmuch as the portion of the vascular system which is thus cut off is much too small to cause such an increase of pressure throughout the whole aortic system, since the vessels leading to other organs might become correspondingly dilated, it must be assumed that in the case of contracted kidney some other hindrance to the circulation occurs throughout more extensive vascular areas. This hindrance would most naturally be sought in the apparatus which normally serves to keep the aortic pressure at its proper height, namely, in the smaller arteries of the body. Whether the condition is caused by nervous stimuli arising in the kidney, or by the action of retained urinary substances upon the vasomotor centres or directly upon the vessel-walls, or whether the heart is excited by nervous stimuli to increased action, we are not at present able to say.

Increase of resistance in the aorta may result from stenosis of this vessel, as occurs in rare cases at the isthmus, or from congenital narrowings of the whole aorta, large aortic thrombi, or from extensive disease of the vessel-wall, in consequence of which the intima is rough and nodular, the entire vessel rigid, inelastic, and unyielding; or, finally, from a general dilatation of the vessel, whereby eddies are formed in the blood-stream.

Lowering of the total resistance in the systemic circulation is possible through the relaxation of the tone of a large part of the arteries, and this event may happen when the vasomotor centre is paralyzed, or when the cervical cord is divided or partly destroyed through any other process. Since the blood, in this case, flows abnormally quickly from the arteries into the veins, the difference in blood-pressure between the arteries and veins is lessened, the current becomes slower, the heart receives too little blood during diastole, and, finally, the circulation may come to a standstill.

Increase of the resistance in the pulmonary circulation occurs most frequently as the result of disease of the lungs and pleura. Adhesions of the pleura, as well as spinal curvatures, which hinder the expansion of the lungs and their change of volume during inspiration, thereby depriving the circulation of an efficient aid, may cause such increase of pulmonary resistance. Of great influence, moreover, are such affections of the lung as idiopathic emphysema, retractions and indurations of the lung, and destruction of lung-tissue—all of which lead to the obliteration of a portion of the pulmonary capillaries; further, compression of the lung through pleural exudate; and, finally, compression of the pulmonary arteries by aortic aneurism or by tumors.

If the hindrance is only slight, the blood may make for itself a new passage to the left heart without any increase of pressure; the rate of the current in the blood-vessels which are unobstructed alone being increased. Greater obstacles cause an increase of pressure in the pulmonary artery and the right heart, and if the condition persists for some time the right ventricle through increased exertion may become hypertrophic. This can occur, however, only when the heart-muscle is adequately nourished and when the mass of the blood is not diminished to correspond to the diminution of the area of the pulmonary vessels. If the right heart is not able to overcome the obstacles in the pulmonary circulation, the blood is dammed back upon the right heart, and eventually upon the systemic veins.

An *increase of the pressure in the right side of the thorax* hinders the entrance of the venous blood into the right heart, and causes an accumulation of blood in the systemic veins. A sudden increase of pressure may cause a retrograde flow of blood into the neighboring veins.

According to the investigations of *Romberg*, *Pässler*, *Bruhns*, and *Müller*, pneumococci, diphtheria-bacilli, and the Bacillus pyocyaneus injure the circulatory apparatus of the rabbit (leaving out of the question the dilatations of the heart that occur particularly in diphtheria), in that they cause paralysis of the vasomotor centres in the medulla. This paralysis leads to a diminution of the arterial blood-pressure and to a change in the distribution of the blood. The splanchnic vessels become overfilled, the vessels of the brain, skin, and the muscles become empty. The heart is not concerned in this disturbance of the circulation. In general, it is affected secondarily as a result of the deficient flow of blood due to the vasomotor paralysis. A *central paralysis of the vasomotors* is also responsible for the circulatory disturbances occurring in the *acute infections*; and is the chief cause of the failure of the circulation.

The observation that hypertrophy of the heart follows different diseases of the kidneys has been interpreted in various ways. Some writers seek the cause in an increase of the volume of the blood (*Traube*, *Bamberger*), others (*Senator*, *Ewald*) believe it to be due to the changed character of the blood, while others (*Gull* and *Sutton*) ascribe it to a widespread change in the walls of the small arteries. *Buhl* holds that it is due to the over-nourishment of the heart. According to the investigations made up to the present time, there can be no doubt that the hypertrophy of the heart in diseases of the kidney is dependent upon an increase of the aortic pressure. This increase is best explained by an increase of the resistance in the small arteries of the entire body, due to the contraction of the small arteries. This contraction must be brought about either through the direct action of the urinary substances contained in the blood or by some reflex stimulus from the kidneys, or finally by some influence exerted upon the vasomotor centre. It is possible that the heart also may be excited to increased activity.

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II. Local Hyperæmia and Local Anæmia.

§ 36. To the blood is assigned the function of supplying all the organs and tissues of the body with nourishment. The cells and cellular structures of which the various tissues are composed are able to maintain their existence without the advent of fresh nutritive material only for a short time; and for this reason the majority of the tissues are supplied with blood-vessels, and those not possessing vessels of their own are placed in the most intimate connection with vascular structures.

The demands of the different tissues for blood are not always the same, and there is consequently in the various tissues a corresponding increase or decrease in the afflux of blood and in the amount of blood contained within an organ or tissue at any given moment. An organ rich in blood is designated as **hyperæmic**; one poor in blood as **anæmic**.

The regulation of the amount of blood which an organ receives under physiological conditions is brought about by a change of the resistance in the afferent arteries; and this change is effected entirely through a variation in the calibre of the arteries. Since the total mass of the blood in the body is not sufficient to fill all the vessels at the same time, an extra supply of blood to one organ is possible only by supplying a less amount of blood to other parts. The change in the calibre of an artery is determined, aside from the blood-pressure, by the elasticity of the artery-wall and the degree of contraction of its smooth muscle-fibres. These fibres are the regulating element; their activity is dependent partly upon influences affecting them directly, and partly upon nervous influences from the intravascular plexuses and from the vasomotor centres in the medulla oblongata and in the spinal cord, some of these stimulating, others inhibiting the muscular action.

When the departures from the average blood-supply of any part of the body overstep the physiological limits, or if such variations arise without physiological causes, or are unduly prolonged, the condition is spoken of as **pathological hyperæmia** and **pathological anæmia**. These conditions are in part brought about by the same regulating mechanism which governs the normal blood-supply of an organ.

Hyperæmia of an organ is caused **under pathological conditions** either by an increase in the arterial supply or through an obstruction and damming-back of the venous outflow; and there are distinguished, accordingly, two forms, an *active* or *congestive* (*arterial*) *hyperæmia* and

a *passive* or *stagnation* (*venous*) *hyperæmia.* **Active hyperæmia** arises through an *increase of the afflux of blood* (*congestion*), and may be either *idiopathic* or *collateral.* The first of these plays the more important rôle. It depends upon a relaxation of the muscular tunics of the artery, which may be brought about either by paralysis of the *vasoconstrictors* (*neuroparalytic congestion*), or through a *stimulation of the vasodilators* (*neurotic congestion*), or through direct *weakening* and *paralysis of the muscles* (as, for instance, by heat, bruising, action of atropine, brief interruptions of the blood-current), or, finally, through a *diminution of the external pressure exerted upon the vessels. Collateral hyperæmia* is merely the result of a diminished flow of blood to other parts. It occurs first in the immediate neighborhood of the parts whose blood-supply is lessened; later, the blood may be driven also to such other more distant organs as may require it.

Active hyperæmia is characterized by a more or less *marked redness* and *swelling* of the part, which are very striking in tissues rich in blood-vessels. The blood flows through the widened channels with increased velocity, and gives to the tissue the color of arterial blood. Superficial tissues which are exposed to cooling become as a result of the increased blood-supply warmer than the neighboring tissues which are less richly supplied.

Passive Hyperæmia arises through the *retardation* or *obstruction of the flow of blood from the veins.* A *general passive congestion of the systemic veins* occurs in those cases in which, through weakness of the heart's action, valvular insufficiency or stenosis, or obstructions to the pulmonary circulation, the emptying of the large veins into the right heart is hindered. In the pulmonary circulation stagnation of the blood-stream may be brought about by any cause hindering the outflow of blood from the lungs, particularly valvular lesions of the left heart, weakness of the left side of the heart, and, more rarely, obstructions in the systemic arteries. Not infrequently such a stasis of the pulmonary circulation may reach such a degree that the blood is dammed back into the right heart, and into the veins of the systemic circulation (see §§ 34 and 35).

Local passive congestion may arise directly from the fact that the progress of blood through the veins is not adequately supported by the activity of the muscles and the aspiration of the blood from the veins during the inspiratory enlargement of the thorax. The absence of the first factor is most apparent in the case of the branches of the inferior vena cava; as, for example, in individuals who pass a large part of their time sitting or standing without active bodily exercise, so that the emptying of the deep-seated venous branches into the vena cava is dependent almost wholly upon the activity of the vein-walls, which by virtue of their elasticity and contractility work against the pressure of the column of blood resting upon them. The absence of the inspiratory aspiration of the venous blood may, on the other hand, make itself felt in disturbance of inspiration through inflammation or other disease-processes of the lungs or pleura.

A further cause of local passive hyperæmia consists in the narrowing or closing of individual veins, as in the case of compression, ligation, formation of thrombi (§ 38), and the invasion of the veins by new-growths. For example, the pregnant uterus or a pelvic tumor may compress the pelvic veins, a thrombus may obstruct the cerebral sinuses or the femoral or portal veins, or a sarcoma of the pelvis may grow into the large pelvic veins.

When through the above-mentioned processes or through ligation, single veins become occluded, the effect of the occlusion is often very insignificant, inasmuch as the veins concerned may possess free communication with other veins, so that but slight obstruction is offered to the outflow of the blood. If, on the other hand, the occluded vein possesses no collateral communications, or very small ones which are inadequate for the passage of the blood—as, for instance, is the case with the main divisions of the portal vein, the sinus of the dura mater, the femoral and the renal veins—there results a more or less marked passive congestion in the area supplying the given vein.

The effect of an obstacle to the outflow of blood shows itself first in that portion of the vein lying between the obstruction and the periphery, the blood-current becoming slowed or checked entirely, while at the same time there follows a progressive filling and dilatation of the veins through the continued afflux of blood from the capillaries. If through the counteractive effect of the increasing tension of the elastic and contractile vein-walls the obstacle is overcome, the circulation is maintained, and the blood flows toward the heart through the channels which it still finds open. Not infrequently the small veins thus called upon to perform this increased labor become gradually much dilated, and are converted into larger veins. When the obstacle cannot be overcome and communicating vessels capable of dilatation are not present, the circulation comes to a standstill, and a condition of stasis (§ 40) or thrombosis (§ 38) is produced in the obstructed vessel and its tributaries.

If the congestion within a venous area extends to the capillaries, so that they become overfilled with blood, the affected tissue becomes *blue-red* or *cyanotic*, exhibiting at the same time a certain degree of *swelling*.

Both active and passive hyperæmia, observed during life, may, after death, show a very different appearance, and not infrequently disappear entirely. This is especially the case in the active hyperæmias of the skin, in part also in those of the mucous membranes. This is dependent upon the fact that the tissues, put upon the stretch by the dilatation of the capillaries, contract upon the latter, after the stoppage of the circulation, and by their counter-pressure drive the blood from the capillaries into the veins. In this way a tissue which was red during life may become pale after death. On the other hand, tissues which during life were pale or at least showed no especial redness, may after death take on a blue-red color. This takes place particularly upon the sides and back of the trunk (in those parts not pressed upon by the body-weight), on the neck, and the posterior aspects of the extremities of cadavers lying upon their backs; and is to be explained by the fact that after death the blood sinks to the most dependent parts of the body, and fills not only the veins, but finally also the capillaries. This phenomenon is known as **post-mortem hypostasis,** and the areas of discoloration as "**death-spots**" or **livores.** They appear within about three hours after death, and are the more pronounced the greater the amount of blood contained in the skin and subcutaneous tissues at the time of death.

In the internal organs post-mortem hypostasis is particularly noticeable in the pia mater, the dependent veins being usually more markedly distended with blood than those situated higher. In the lungs the settling of the blood causes an engorgement not only of the veins, but also of the capillaries.

If the general circulation during life, as a result of cardiac insufficiency, is imperfect, and there results a general passive congestion, the

blood may also collect in the dependent portions of the body, partly because it is not driven out of them, and partly because it sinks into these parts from those situated on a higher level. This phenomenon is also known as **hypostasis**, and occurs particularly in the lungs (*hypostatic congestion*).

For the observation of the circulation and its disturbances during life the tongue or the web of the curarized frog, properly spread upon a glass plate, may be used (*Cohnheim*, *Virch. Arch.*, Bd. 40). This may be done in a very simple manner by drawing the frog's tongue over a cork ring, which is cemented to a glass plate, and fastening it to the sides of the ring with pins. The pulsating arterial current and the continuous venous stream possess a clear zone of blood-plasma, in both the normal and the quickened circulation. If, through the ligation of the efferent veins of the tongue, passive congestion is produced and the current slowed, the plasma-zone in the veins is lost, and both veins and capillaries become greatly distended with accumulated red cells. After a certain time the tongue swells as the result of an infiltration with transuded fluid.

According to the investigations of *von Landerer* ("Die Gewebsspannung," Leipzig, 1884), the wall of a capillary vessel embedded in tissue supports only from one-third to one-half of the blood-pressure. The remaining portion is borne by the tissues, which afford an elastic resistance, and thereby maintain the tension which is necessary to keep the blood in motion. In both active and passive hyperæmia both the tissue-pressure and the tissue-tension are increased; in anæmia they are diminished.

§ 37. **Local anæmia** or **ischæmia**, the lack of proper blood-supply to a tissue, is always the result of a diminution in the afflux of blood. If the total mass of the blood is normal, the cause of the anæmia is purely local; if there is a general poverty of blood, the local anæmia, in part at least, is secondary.

The **pathological diminution in the blood-supply** to an organ is at times merely the result of an *abnormal increase of the arterial resistance*, due to the contraction of the circular muscular coat. According to Stricker, Steinach, and Kahn, the capillaries also possess a power of contractility which is under the influence of the nervous system. In other cases *pathological obstructions*—such as compression of the arteries, narrowing of the arterial lumen through pathological changes in the vessel-walls, deposits on the inner surfaces of the arteries, occlusion of the vessels by emboli (see Fig. 2, p. 65), etc.—may act as hindrances to the blood-stream.

The immediate result of the *narrowing of an artery* is always a slowing and diminution of the blood-stream beyond the point of constriction. *Complete occlusion* of an artery brings the circulation beyond the obstruction to an immediate standstill. If back of the point of constriction or occlusion the artery is provided with large arterial communicating branches—the so-called *arterial collaterals*—the disturbance of the circulation may be compensated by an increased afflux of blood through the collateral arteries; and this compensation is the more complete the larger and the more distensible are the collaterals. If the narrowed or occluded artery possesses no collateral branches in its area of distribution—if it is a so-called *terminal artery*—the slowing or cessation of the circulation beyond the point of obstruction or occlusion cannot immediately be done away with, and the affected vascular area becomes partly or wholly emptied of blood, in that, through the contraction of the arteries and the pressure of the tissue on the capillaries and veins, the blood is almost wholly driven out of the area supplied by the obstructed artery. Frequently there occurs after a time an afflux of blood from the neighboring capillaries.

When the current and the pressure beyond a *constricted point* have

sunk to a certain minimum, the driving force gradually becomes unable to propel the mass of blood. The red corpuscles, in particular, cease to move, and collect in the veins and capillaries, so that the *area supplied by the artery in question becomes again filled with blood*; only not with circulating, but with stagnant blood. *The same thing occurs when, after complete occlusion of a terminal artery*, the blood slowly and under low pressure enters the vessels of the affected area from small arteries incapable of adequate enlargement, or merely through anastomosing capillaries. Finally, an accumulation of blood within the anæmic area may also occur by a reflux from the veins. This takes place when the intravascular pressure within this area has sunk to nothing in the arteries and capillaries, while in the veins a positive pressure exists. A condition of passive congestion in the veins favors such a reflux.

A further cause of anæmia of one organ may be found in the abnormal congestion of other organs, as in that case the total mass of the blood is not sufficient to supply adequately the remaining organs. Such an anæmia is designated *collateral anæmia*.

All *anæmic tissues* are characterized by *paleness*. At the same time they are flabby, not turgescent, and show their individual color more distinctly.

The **significance of ischæmia** lies especially in the fact that, on account of the need of the tissues for a continuous supply of oxygen and food-material, the persistence for a certain length of time of the condition of imperfect blood-supply brings about *tissue-degenerations* (compare § 1). Total arrest of the blood-supply leads in a short time to the *death* of the tissue involved. If the blood comes to flow anew into the degenerating and dying tissues in the area of distribution of an obstructed vessel, and there stagnates, an extravasation of blood into the tissue may take place, leading to the formation of a *hæmorrhagic infarct* (compare § 44).

The rapidity and completeness of the *development of a collateral circulation* after the occlusion of an artery depends upon the size and distensibility of those vessels which are in communication with those of the anæmic area. If these are numerous and distensible, the anæmic area is soon again supplied with an approximately normal volume of blood. If this is not the case the disturbance of the circulation is more slowly compensated; and the stasis and increased pressure are found to extend farther back from the point of obstruction toward the heart, so that a collateral hyperæmia occurs in vessels situated farther back toward the heart. In the further course of the process of re-establishing the circulation the resulting increase of volume and velocity remains confined to such vessels as communicate with the area of the obstructed artery, that is, confined to the capillary and arterial anastomoses, where the increase of volume and velocity become permanent. This leads further to a lasting dilatation of the vessels concerned, and at the same time to an increase in the vessel-walls, not only in thickness, but also in length, as is evident from the increased tortuosity of the vessels. According to *Nothnagel*, the phenomenon of the increase in thickness of the walls of the anastomosing arteries may be demonstrated in the case of rabbits in about six days after the ligation of an artery; and after the ligation of large vessels in their continuity, the small arteries which carry on the collateral circulation become changed in the course of a few weeks, into quite capacious, thick-walled arteries.

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III. Coagulation, Thrombosis, and Stasis.

§ 38. Upon the *death of the individual* the **blood** contained in the heart and great vessels sooner or later **coagulates** in part, and there arise those formations which are known as **post-mortem clots.** If the clotting occurs at a time when the red blood-cells are still evenly distributed in the blood, the whole mass of the blood becomes coagulated, forming soft, dark-red masses of coagulum which are known as **cruor.** If before the clotting there occurs, through the sinking of the red cells, a separation of the blood into two layers—a substratum rich in red blood-corpuscles, and an upper fluid layer containing none and consisting only of the plasma—then, if the latter coagulate, there will be formed soft, gelatinous, light-yellow, elastic lumps and stringy masses having a smooth surface and not adherent to the vessel-wall, which are known as *lardaceous clots* or as *fibrinous deposits.* These contain the same fibrin threads (Fig. 12) and scattered red and white blood-cells. Through the inclusion of red cells in these formations, they may present in parts a red or reddish-black color; if large numbers of leucocytes are present, they may have a whitish color.

FIG. 12.—A lardaceous clot from the cadaver. (Formalin, hæmatoxylin, and eosin.) × 500.

When blood is drawn from an artery or vein and received into a vessel, *coagulation* will occur within a short time, as the result of the adhesion of the fluid to the sides of the receptacle. The entire blood-mass becomes changed into a soft coherent mass. When freshly drawn blood is

beaten with a solid body, the surface of the latter becomes covered in a very short time with felt-like *fibrin*. *If within the body large quantities of blood pass out into the tissues*—as, for example, into the pericardium or into the lungs—*coagulation* may occur here likewise, and the extravasated blood may in this way acquire a firm consistency (Fig. 13, *d*).

Under certain conditions there may be formed *within the heart or blood-vessels during life, firm deposits*, which in part are similar to cruor, and in part to the fibrin-masses formed by whipping the blood. These formations are known as **thrombi**, and the process which leads to their formation as **thrombosis**. According to their color they may be distin-

FIG. 13.—Coagulated blood in a fresh hæmorrhagic infarct of the lung. (Müller's fluid; hæmatoxylin and eosin.) *a*, Alveolar septa without nuclei, containing capillaries filled with dark bluish-violet, homogeneous thrombus-masses; *b*, septa containing nuclei; *c*, vein filled with red thrombus; *d*, d_1, alveoli filled with firm blood-clots; *e*, alveoli filled with serous fluid, fibrin, and leucocytes. × 90.

guished as *red*, *colorless* or *white* (that is, yellow or grayish-white), and *mixed thrombi*.

The **coagulation of the blood** is a peculiar process, difficult of exact interpretation. **Histologically**, it is characterized, both in extravascular clotting (Fig. 13, *d*, d_1) and in intravascular as well (Fig. 14), by the formation of little *rods and threads* between the red cells, at one time arranged in a meshwork, at other times in stellate or fascicular groups around centres. These little rods and fibres are known as **fibrin**; and are in part smooth and shining, in part covered by little granules, or partly interrupted by granules, or are composed entirely of such collected together. Besides the threads there occur also *free granules*, *granular masses*, and *blood-plates* of varying size and form; and not infrequently such formations lie in the centre of the fibrin-stars. At times the stellate and fascicular forms of fibrin are found arranged about leucocytes or attached to endothelial cells of the intima of the vessel.

In the red blood-cells there occur here and there degenerative appearances, in the form of plasmolysis, plasmorrhexis, and plasmoschisis. In *plasmolysis* or *erythrocytolysis* there occurs a passage of soluble substances from the red cells into the blood plasma, so that the red cells become smaller, and the so-called microcytes and red blood-cell "shadows" are produced. At the same time individual cells may become swollen.

In *plasmorrhexis* or *erythrocytorrhexis* and in *plasmoschisis* or *erythrocytoschisis*, bright, shining globules arise from the red cells, or the latter

become covered with little prickle-like projections, or come to resemble mulberries, or send out protoplasmic processes. Through the snaring-off of these prominences round, disc-like, angular, or thread-like bodies are formed, which are partly homogeneous and partly finely granular, and not infrequently enclose larger shining bodies. Finally, the red cells may break up into disc-like or globular pieces, and finally into granules. The formations known as *blood-plates* are for the greater part *peculiarly formed products of plasmorrhexis and plasmoschisis of the red cells;* and it is possible to distinguish among them those which are colorless, those containing hæmoglobin, and homogeneous and granular forms.

In fresh coagula, changes cannot usually be demonstrated in the *colorless corpuscles of the blood;* but in the later course of the process degenerative appearances are found in these also; and products may thereby be produced resembling those arising through the disintegration of the red blood-cells designated as blood-plates.

Between the destruction of the red blood-cells, respectively the formation of the blood-plates, and the coagulation of the blood, both extra- and intravascular, there exist undoubtedly close relations; that is, coagulation is set into action through the occurrence of changes in the red cells as above described. According to our present knowledge, it must be assumed that many red cells, probably the oldest ones, very easily suffer such changes, so that, for example, adherence to a diseased portion of the vessel-wall, which is prevented by the normal condition of the intima, is sufficient to cause a disintegration of certain red cells, with formation of blood-plates, and later coagulation and thrombus-formation. The origin of coagulation has also been regarded as due to plasmolysis and plasmorrhexis of the leucocytes; further, similar degenerations of the endothelium may also induce coagulation. The possibility that the endothelial cells play a certain part in the origin of coagulation cannot be excluded, but it must be emphasized that the degenerative changes ordinarily preceding coagulation cannot be demonstrated in these cells. The facts brought forth, particularly by Hauser and Zenker, that the fibrin-threads not infrequently are attached to endothelial cells, or leucocytes, or to the remains of such cells, do not prove that these are the *exciters* of coagulation, or that they offer *material* for the formation of fibrin; inasmuch as the deposit of the fibrin upon these cells may be due to purely mechanical causes.

FIG. 14.—Bundles and star-shaped clusters of fibrin threads within a blood-vessel. (Fibrin stain.) Preparation taken from an inflamed tracheal mucous membrane. × 500.

The **chemical processes** concerned in coagulation cannot at present be explained. It is assumed that for its occurrence the presence of a *fibrinogenic substance, a ferment* (*thrombin*), and certain *salts*, particularly *calcium salts*, is necessary; and that the fibrinogenic substance is an albuminoid body belonging to the *globulins*, which is present in the blood-plasma; while the ferment is produced by the cells. According to A. Schmidt, thrombin is derived from a parent-substance, pro-

thrombin which becomes active under the influence of a *zymoplastic substance.* By means of the thrombin there is formed, in an as yet unknown manner, from the globulins pre-existing in the alkaline solution, a greatly swollen albuminoid body, which is precipitated by the calcium salts contained in the plasma. In the process of coagulation we must, therefore, recognize two stages, namely, the stage of the production of the fibrin-ferment, and the stage of the action of the ferment or coagulation proper.

Morawitz is also of the opinion that fibrin-ferment arises through the coöperation of several substances, *thrombogen, thrombokinase,* and *calcium.* The substance designated as thrombokinase is identical with the zymoplastic substance of Schmidt and behaves in the same way as a ferment.

FIG. 15.—Section through a red thrombus formed in one of the veins of the thigh-muscles, after occlusion of the femoral vein. (Müller's fluid; hæmatoxylin.) *a*, Fibrin-threads; *b*, leucocytes and granular masses. × 250.

The **red thrombus** *is formed under such conditions as the complete stoppage of the circulation or a marked slowing of the same,* and comprises the total mass of the red cells (Fig. 15). The precipitated fibrin forms granules (Fig. 15, *b*) and threads (*a*). In fresh clots in small vessels, it is not infrequently possible to demonstrate after death, by means of special methods, the presence of bundles and star-shaped clusters of fibrin-rods (Fig. 14), which radiate from centres of coagulation. In such cases, however, it is often impossible to distinguish with certainty to what extent the coagulation is intravital or to what extent post-mortem. Such form of coagulation is most frequently observed in inflamed tissues, and the conclusion is warranted that changes in the blood occurring in such inflammatory areas are the cause of this variety of fibrin-formation. Since these thrombi often enclose very few red blood-cells (Fig. 14) and thereby present a pale appearance, it is evident that the red blood-cells for the greater part must have become disintegrated.

Immediately after its formation the red thrombus is soft and rich in the fluids of the blood; later it becomes tougher, denser, and more dry, as the fibrin contracts and squeezes out a portion of the fluid. At the same time it becomes paler, brownish-red or of a rust-color, inasmuch as the blood-pigment undergoes changes similar to those occurring in extravasations.

The **cause of the ante-mortem intravascular coagulation** is to be found either in an *increase in the production of fibrin-ferment or fibrinogenic substances* or in a *diminution of the power possessed by the normal vessel-wall of inhibiting coagulation.* Under certain conditions the more marked adhesion of the blood to a degenerated area in the vessel-wall may in itself be sufficient to induce coagulation. This occurs accordingly in ligated vessels, when the endothelium at the point of ligation is injured; but in the case of a slight injury to the vessel-wall and the blood, clotting may not take place (Baumgarten).

White, mixed, and often distinctly **laminated thrombi** *arise in the flowing blood,* and consist of masses of yellowish color, or of various shades of red, or of alternating layers of red and white. The microscopical examination shows them to consist of granular and thread-like masses (Figs. 16 and 17), leucocytes, and red cells, which in varying pro-

FIG. 16. Section from a mixed thrombus rich in cells. (Müller's fluid, hæmatoxylin.) *a*, Red blood-cells; *b*, granular masses; *c*, reticular fibrin containing many leucocytes; *d*, threads of fibrin in parallel arrangement. × 200.

FIG. 17.—Section from a white thrombus containing but few cells. (Müller's fluid; hæmatoxylin.) *a*, Granular masses; *b*, fibrogranular fibrin forming a net-like reticulum; *c*, fibrin-threads in parallel arrangement. × 200.

portion and arrangement make up their structure. White thrombi may consist almost entirely of granular masses (Fig. 17, *a*) and fibro-granular fibrin, which in some cases is arranged in a meshwork (*b*), in others in fibres running nearly parallel (*c*) which enclose few leucocytes. In other cases the number of cells may be much greater. In mixed thrombi (Fig. 16), granular fibrin (*b*), more rarely hyaline masses, thready fibrin (*c*, *d*), and red blood-cells (*a*), in varying proportion and in alternating stratification, constitute the thrombus-mass, and all of these elements enclose more or less numerous, often many leucocytes. The colorless portions of mixed thrombi consist essentially of fibrin, fluid, and leucocytes, but they often contain also numerous decolorized red blood-cells.

The *fibrogranular masses* which form part of the structure of the thrombus are composed of **precipitated fibrin.** The *granular* and *hyaline masses,* on the other hand, probably arise directly from the **products of the plasmoschisis and plasmorrhexis of the red blood-cells,** in particular from the **blood-plates.** In large thrombi they often show a coral-like arrangement.

The **causes of the formation of white and mixed thrombi** are especially: *changes in the intima of the heart and the vessels* and *diseases of the vascular apparatus,* that lead to a *general or local slowing or irregularity of the blood-stream.*

The **formation of thrombi** may be studied directly, in suitable subjects, under the microscope, both in the case of cold-blooded and warm-blooded animals; and the observations made in this line, especially by *Bizzozero, Eberth, Schimmelbusch,* and *Löwit,* have led to very important results.

When the blood flows with normal velocity through a blood-vessel, there may be

seen under the microscope a broad, homogeneous red stream in the axis of the blood-vessel (Fig. 18, *a*), while at the sides there lies a clear plasma-zone (*b*) free from red cells. This may be observed in the arteries, veins, and large capillaries, but is best seen in the veins, while in the small capillaries, which are just large enough to permit the passage of the red cells, this difference between the axial stream and plasma-zone is not present.

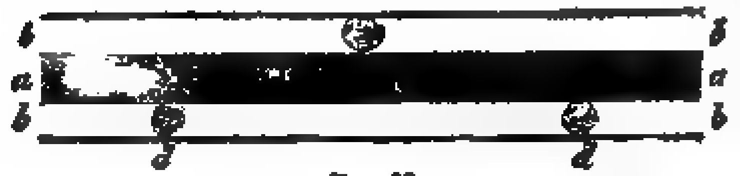

FIG. 18.

FIG. 19.

FIG. 20.

FIG. 18.—Rapidly flowing blood-stream. *a*, Axial stream; *b*, marginal zone with isolated leucocytes, *d*. (After Eberth and Schimmelbusch.)

FIG. 19.—Moderately slow blood-stream. *a*, Axial stream; *b*, peripheral zone with numerous leucocytes, *d*. (After Eberth and Schimmelbusch.)

FIG. 20.—Markedly slow current. *a*, Axial stream; *b*, peripheral stream with blood-plates; *c*, collection of blood-plates; *d*, d_1, leucocytes. (After Eberth and Schimmelbusch.)

In the axial stream the different constituents of the blood-stream are not recognizable; in the plasma-zone there appear, from time to time, white blood-corpuscles (Fig. 18, *d*) which roll slowly on along the vessel-wall.

If the blood-stream becomes retarded to about the degree that the red cells of the axial stream are indistinctly recognizable (Fig. 19, *a*), the number of white corpuscles which roll slowly along in the plasma-zone, at times adhering to the vessel-wall, becomes constantly increased (Fig. 19, *d*), so that they finally come to lie in great numbers in this zone.

If the current is still further retarded so that the red cells become plainly recognizable (Fig. 20, *a*), there appear in the peripheral plasma-zone, in addition to the colorless blood-corpuscles (*d*), also blood-plates (*b*), which increase more and more in number with the progressive retardation of the current, while the leucocytes again become diminished in numbers. When total arrest of the blood-current finally occurs, there follows a distinct separation of the corpuscular elements in the lumen of the vessel.

If, in a vessel in which the circulation is retarded, the intima is injured at a certain point by compression or crushing, or by means of chemical agents, as corrosive sublimate, nitrate of silver, or sodium chloride, and if the lesion of the wall does not lead to a complete stoppage of the circulation, *blood-plates* may be seen *adhering to the injured portion of the wall*; and in a short time the injured spot is covered with many layers of the same (Fig. 20, *c*). Often, more or less numerous *leucocytes* (d_1) become embedded in this mass, and their number is the greater the more numerous these are in the plasma-zone. Under certain conditions they may be very numerous and partly cover up the blood-plates. In case of great irregularity of the circulation or more severe changes in the vessel-wall, *red cells* may also drop out of the circulation and *become adherent* to the vessel-wall or the colorless deposit already formed. Not infrequently portions of the thrombus-mass are again torn loose, in which case a new deposit of blood-plates occurs. The vessel may finally be closed as the result of a long-continued deposit of the blood-elements.

When at any point blood-plates in large numbers have become adherent to the vessel-wall, they become after a time coarsely granular at their centre, and finely granular or homogeneous at their periphery, and become fused together into one compact mass. The final result of this process is the formation of a colorless *blood-plate thrombus*, within which more or less numerous *leucocytes* may be imprisoned. Eberth designates the sticking together of the blood-plates as *conglutination*, their fusion into a coherent thrombus-mass as *viscous metamorphosis*.

According to the investigations of *Gutschy* the first steps of coagulation consist in the precipitation of a gelatinous mass; and to this "*primary fibrin-membrane*" the blood-plates and later the other formed elements of the blood catch, and may remain fastened.

If we compare the observations made upon warm-blooded animals by *Bizzozero*,

Eberth, and *Schimmelbusch*, and more recently by *Löwit* and *Gutschy*, with the histological findings in thrombi occurring in the human subject, we are warranted in drawing the conclusion that the formation of thrombi in the circulating blood of man occurs in part in the same way as that observed in the lower animals. Thrombosis is, therefore, directly dependent upon two causes: namely, **disturbances of the circulation**, particularly *retardation of the current and the formation of eddies which drive the blood-plates against the vessel-wall;* and **local changes in the vessel-walls.** It is also probable that thrombosis is favored by **pathological changes in the blood.** From the variety of conditions under which thrombosis in man occurs, we must assume that at one time one cause, at another time another, plays the chief part in the formation of the thrombus, or that all three may take an equal part in the process.

If a blood-plate thrombus or a conglutination-thrombus has formed at any point, *coagulation* may subsequently occur, yielding fibrin-threads which enclose a greater or less number—often large number—of the cellular elements of the blood. *Conglutination* and *coagulation may occur in combination;* and the frequency with which this comes to pass, judging from the composition of the thrombi occurring in man (Figs. 16 and 17), seems to denote the fact that fibrin-ferment is produced during the formation of the blood-plate thrombus, and that consequently, in the neighborhood of the conglutinated blood-plates, processes of coagulation occur in the adjacent plasma-zone of the blood-stream. If white corpuscles alone are circulating in this zone, the mass of coagulum is white (Fig. 17) and encloses a greater or less number of red cells; if red corpuscles also circulate in the peripheral zone, or if the coagulation extends into the red axial stream, mixed thrombi will be formed (Fig. 16).

In the place of blood-plates whole red blood-cells may be fused together by agglutination (*Flexner*) and so form hyaline thrombus-masses. If in marasmic individuals, as not infrequently happens, or in those who have been subjected to some traumatism, extensive thrombosis occurs, this occurrence is probably connected with a ferment-intoxication (*Köhler, von Düring*); and the local disturbances of circulation only decide the location of the coagulation. *Vaquez* is of the opinion that infections play a very prominent rôle in the origin of cachectic thrombi. It is probable that the thromboses occurring in cases of chlorosis are dependent upon changes in the blood.

According to *Naunyn, Franken, Köhler, Plosz, Gyorgyai, Hanau*, and others, a more or less extensive thrombosis may be produced by the injection into the blood-vessels of laked blood, solutions of hæmoglobin, salts of cholic acid, ether, and other substances; yet the results of these experiments are not constant (*Schiffer, Högyes, Landois, Eberth*), and coagulation may not occur. The probability of effecting coagulation is proportionate to the degree of disturbance produced in the blood by the substance injected.

According to *Arthus* and *Pagès*, the blood flowing from the veins becomes incapable of coagulating spontaneously if sodium oxalate, sodium fluoride, or soaps are added to it in such quantities that the mixture contains 0.07–0.1 per cent of the oxalate, or about 0.2 per cent of the fluoride, or 0.5 per cent of soap. These salts all act by precipitating the calcium salts. If to blood, kept fluid by treatment with oxalic acid, one-tenth of its volume of a one-per-cent solution of calcium chloride is added, coagulation occurs in six to eight minutes, and the calcium salts pass into the combination of the fibrin-molecule. The fibrin-ferment can act upon the fibrinogen only in the presence of calcium salts. Under the influence of the fibrin-ferment, and the presence of calcium salts, the fibrinogen undergoes a chemical change which results in the formation of a calcium-compound, fibrin. *Hammarsten*, who holds that the presence of calcium is not necessary for the change of fibrinogen into fibrin, attempts to explain the observation of *Arthus* and *Pagès*, through the assumption that the calcium salts are necessary factors for the conversion of prothrombin into thrombin.

If blood be allowed to flow beneath a layer of oil, into a vessel coated with a film of vaseline, it will not coagulate (*Freund*); and from this it may be assumed that the cause of the coagulation is to be found in the adhesion of the blood to a foreign body.

Bizzozero, in the year 1882, described as a new element of the blood, small, flat, homogeneous structures, which he designated as blood-plates, and regarded as identical with the hæmatoblasts described by *Hayem*. Supported by thorough experimental investigations, he assumed that it was these bodies, which, in breaking up, induced coagulation, and, therefore, denied this to be a property of the leucocytes.

Since their discovery the blood-plates have been the object of an extraordinary number of investigations and have been interpreted by different writers in the most varied ways. About them revolve the disputed questions as to whether they are constant elements of the blood or arise only under pathological conditions, whether they are true cells or represent only disintegration products of the red or white blood-cells, and finally, whether they have any definite relation to the coagulation of the blood. *Rauschenbach, Heyl, Weigert, Löwit, Eberth, Schimmelbusch, Hlava, Groth, Wlassow, Ziegler,*

Arnold, Schwalbe, Deetjen, Deckhuyzen, Kopsch, Argutinski, Bürker, and others have busied themselves with these questions. According to my own views, which agree essentially with those of *Wlassow, Arnold*, and *Schwalbe*, the blood-plates are for the greater part disintegration and extrusion products of red blood-cells; according to the investigations of *Arnold, Schwalbe*, and others similar products may arise also from the colorless cells of the blood. At times they show appearances of motion; but they cannot be regarded as cells. They sometimes contain within them bodies staining similarly to nuclear substance, and these are probably to be referred to the elements of nuclear substance which are present in the red blood-cells. According to *Homer Wright* (*Virch. Arch.*, Bd. 186, 1906) the blood-plates are fragments of the cytoplasm of the bone-marrow giant-cells, and occur only in those vertebrates in whose marrow giant-cells are found. Their number increases or diminishes in proportion to the number of giant-cells. *Cole* (*Johns Hopkins Hosp. Bull.*, 1907) has produced a specific agglutinating serum for blood-plateletes. His experiments appear to speak definitely against a genetic relationship between platelets and red blood-cells.

They are found in normal blood, but in great abundance only under pathological conditions. Without doubt they have an important relation to the coagulation of the blood. *Bürker*, who does not regard the blood-plates as disintegration products of the red blood-cells but as independent formations, is of the opinion that coagulation is dependent upon the typical disintegration of the blood-plates, so that the fibrin-mass which is ultimately formed depends directly upon the mass of disintegrating blood-plates.

Morawitz regards the blood-plates as independent cells (*Deetjen, Deckhuyzen, Kopsch*). According to him, they contain thrombogen and thrombokinase, and it is possible therefore to produce coagulation with the blood-plates alone without the addition of leucocytes or of lymph. *Thrombogen arises probably from the blood-plates alone. The white blood-cells* probably contain no thrombogen, but only *thrombokinase*, which is probably produced by a great variety of cells.

At the present time no pathological significance can be attached to an increase or decrease in the number of the blood-plates. It has been stated that they are increased in leukæmia, afebrile anæmias, and after hæmorrhage, and decreased in febrile conditions and in various intoxications. The failure to fix any definite normal standard (their number being estimated by various authors as 100,000–500,000) does not favor their numerical estimation as an aid in diagnosis.

A. Schmidt, in his work on the blood, published in 1892, in which he collects the results of many years of study on the coagulation of the blood, regards the fibrin-ferment or *thrombin* as a cell-derivative, which arises from an inactive antecedent substance, *prothrombin*, under the influence of certain *zymoplastic substances* which are also cell-derivatives. He likewise regards the *fibrinogenic substance*, or *metaglobulin*, as a product of the disintegration of cellular protoplasm. Therefore, the substances causing coagulation as well as those producing thrombosis must all be regarded as cell-derivatives, and the *red blood-cells in particular are the source of the materials of coagulation.*

According to *Pekelharing, thrombin is a calcium compound of prothrombin* which arises from the cellular elements of the blood; and coagulation consists essentially in the fact that the thrombin carries calcium over to the fibrinogen, whereby the insoluble calcium compound, fibrin, is formed. *Hammarsten*, on the contrary, is of the opinion that *calcium is carried down with the fibrinogen only as a contamination* and has no significance in the change of fibrinogen to fibrin in the presence of thrombin. According to him the *calcium salts are a necessary factor only for the change of prothrombin into thrombin.*

According to *Schmiedeberg* and *Heubner*, there occurs in coagulation a hydrolytic splitting of fibrinogen into fibrin and fibrin-globulin.

Agglutination-thrombi occur in the normal mature placenta, and are important pathologically in placental tuberculosis, a hyaline agglutination-thrombus occurring at the site of the primary lesion of the syncytium (*Warthin, Wollstein*). Similar thrombi play also an important part in the production of focal necroses (*Pearce*).

According to *Corin, coagulation occurs in the blood of the cadaver only when the ferment was present in the blood during life,* and the extent of the coagulation is dependent directly upon the amount of ferment contained in the blood during life. A further formation of ferment does not take place after death, on the other hand, it is probable that there is formed by the vessel-walls a body inhibiting coagulation. Between the blood of those dying suddenly (strangulation) and that of individuals dying slowly there is only a relative difference, depending upon the amount of ferment present. A fluid condition of the blood of the cadaver can, therefore, be of no significance in so far as the diagnosis of the manner of death is concerned.

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See also § 39.

§ 39. **Thrombosis** occurs most frequently in cases of degeneration and inflammation of the intima of the heart and of the blood-vessels, as

FIG. 21.—Polypoid heart thrombi firmly attached between the trabeculæ of the left ventricle. *a*, Thrombus with smooth surface; *b*, thrombus with open cavity of degeneration. (Natural size.)

well as under certain conditions which cause a slowing or stoppage of the circulation—as, for example, compression, narrowing, or dilatation of the vessels, fatty heart, stenosis and insufficiency of the valvular orifices, etc. Perforating wounds of the vessels, crushing of the vessel-wall, and laceration of the intima lead likewise to the formation of thrombi; and thrombotic precipitates are formed also upon foreign bodies lying in the vessels. According to the cause of the injury to the vessel-wall there

may be distinguished: *traumatic, infectious*, and *thermic thrombi*, as well as those *produced by degenerative changes in the wall, foreign bodies*, and *tumor proliferation*. Thrombi occurring in enfeebled individuals with poor circulation (cardiac weakness) are usually designated as *marasmic* or *cachectic*.

Thrombi may be classed also according to their relation to the vessel-lumen. Thus thrombi attached to the wall of the heart (Fig. 21, *a*) or blood-vessel are known as **parietal thrombi**, those situated upon the valves of the heart or veins (Fig. 22, *d*) are termed **valvular thrombi.** In both cases the thrombi may consist only of delicate, translucent, membranous, hyaline deposits; but are often thicker and firmer and project into the lumen of the heart or blood-vessels. Their surface often shows ribbed elevations which are paler than the other portions. A thrombus completely closing the lumen of the vessel is called an **obturating thrombus** (Fig. 22, *a, b*). The coagula first formed are designated as **primary** or **autochthonous**, those subsequently deposited upon these as **induced thrombi.** Through growth by accretion a parietal thrombus may become changed to an obturating one. In this way it not infrequently happens that upon an originally white or mixed thrombus a red one (Fig. 22, *c*) is formed; the thrombosis at the beginning occurring in circulating blood, while later, after the closing off of the vessel, the blood stands still and clots *en masse*. The reverse may occur—that is, upon a thrombus originally red there may be deposited white or mixed coagula—when a red thrombus obturating a vessel becomes smaller by contraction, and thus opens up a channel for the free passage of blood.

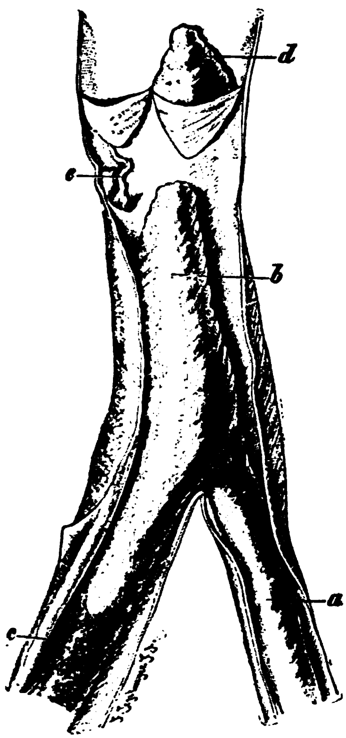

FIG. 22.—Thrombosis of femoral and saphenous veins. *a, b*, Obturating mixed and laminated thrombus; *c*, red thrombus showing peripheral attachment; *d*, thrombus protruding from a valve. (Reduced one-fourth.)

Thrombi may occur in any part of the vascular system. **In the heart** they are formed chiefly in the auricular appendages and in the intertrabecular spaces, as well as upon any diseased spot (Fig. 21, *a*) in the heart-wall. They begin usually in the deep recesses between the trabeculæ, but through continual accretions they form larger masses of coagula which project above the surface in the form of polypoid masses (Fig. 21), which are called **heart-polypi.** They are sometimes more or less spherical in shape, with a broad base; at other times they are more club-shaped; their surface is often ribbed. In rare cases large spherical or knobby thrombi may become loosened; and, in case they cannot pass the ostium, lie free in the corresponding chamber of the heart. Such **free globular thrombi** are sometimes seen in the auricles in cases of stenosis and insufficiency of the auriculo-ventricular orifices, but they are of rare occurrence. After their detachment they may increase in size

through the formation of new deposits of fibrin. Masses of coagula which are deposited upon inflamed valves are known as **valvular polypi.** Parietal and valvular polypi may become very large and fill up a large part of the heart-chambers.

In the arterial trunks thrombi may occur in a great variety of places, particularly behind constrictions and in dilatations. Occasionally in cachectic individuals with a much-degenerated arterial intima, parietal, white, or mixed thrombi, adherent to the surface, are formed in the aorta.

In the veins thrombi are occasionally formed in the pockets of the valves (Fig. 22, *d*), from which they may gradually protrude and develop into obturating thrombi. Often a thrombus may grow from a smaller vein (*a*), where it was primary, into the lumen of a larger vein (*b*). Thus, for example, a thrombus having its origin in a small vein of the lower extremities may finally grow into the inferior vena cava and even reach the heart. Of especial importance, because of the resulting local disturbances, are the obturating thrombi of the femoral veins, the renal veins, the sinus of the dura mater, the venæ cavæ, and the portal veins.

Thrombosis in the smallest vessels is most frequently the result of disease of the surrounding tissues, particularly infectious and toxic inflammations and necrotic processes. The thrombi formed are, for the greater part, hyaline; in their composition the colorless elements of the red blood-corpuscles have the chief share, fusing together into a homogeneous mass. Nevertheless, it may be demonstrated occasionally, by means of proper technique (Weigert's staining method), that they also contain thready fibrin. Thrombi of smaller vessels occur also after burns of the skin (Klebs, Welti, Silbermann) and often in cases of poisoning—for example, with corrosive sublimate (Kaufmann)—and are found especially in the smaller vessels of the lung. They frequently occur in hæmorrhagic infarcts (Fig. 13, a_1). Thrombi originating in the capillaries may develop also into the efferent veins, partly for the reason that through the obturation of numerous capillaries the blood flows more slowly into the veins, partly also for the reason that disintegrating red cells and blood-plates pass into the veins in large numbers.

FIG. 23.—Remains of a thrombus of the right femoral vein occurring three years before death. *a*, Obliterated portion of the vein (the right common iliac artery was also obliterated); *b*, *c*, *d*, connective-tissue cords in the lumina of the vein and its branches; *e*, fresh thrombus. (Natural size.)

The **first deposits** in the formation of a parietal thrombus consist of delicate, translucent, or whitish layers. The **fully formed thrombus** is a rather firm, dry mass, firmly adherent to the inner surface of the vessel or heart, and in color and structure varying according to the conditions mentioned above. Thrombi, originally soft and moist, undergo in time a process of **contraction,** and thereby become firmer and more dry. By means of such contraction vessels closed by obturating thrombi may again become opened for the passage of the blood.

In case of marked contraction, the fibrin, blood-plates, and the red blood-cells may become changed into a firm mass, which may remain in

FIG. 24.—Obliteration of a pulmonary artery by connective tissue after embolic plugging of its lumen. (Müller's fluid, hæmatoxylin, and eosin.) *a*, Artery wall; *b*, connective tissue filling the vessel-lumen; *c*, *d*, newly formed blood-vessels. × 45.

this condition for a long time, become firmly adherent to the vessel-wall, and finally undergo **calcification.** This may occur in both valvular heart-thrombi and thrombi located in the vessels. The chalky concretions formed in this manner in the veins are known as **phleboliths**; those occurring more rarely in the arteries as **arterioliths.**

Contraction and calcification are relatively favorable sequelæ of thrombosis. Much less favorable are the more frequent processes of degeneration occurring in thrombi, which are known as simple and as puriform or yellow septic softening. In **simple softening** the central portion of the thrombus becomes changed into a grayish-red, or gray, or grayish-white grumous mass, consisting of disintegrated and shrunken red corpuscles, pigment-granules, and colorless, granular débris. If the softening extends to the superficial layers, and if there is at the same time a certain strength of blood-current in the neighborhood of the thrombus, the products of disintegration may be swept along into the circulation. If thereby larger pieces become loosened and transported by the blood-stream, arterial emboli will be produced (see Fig. 2).

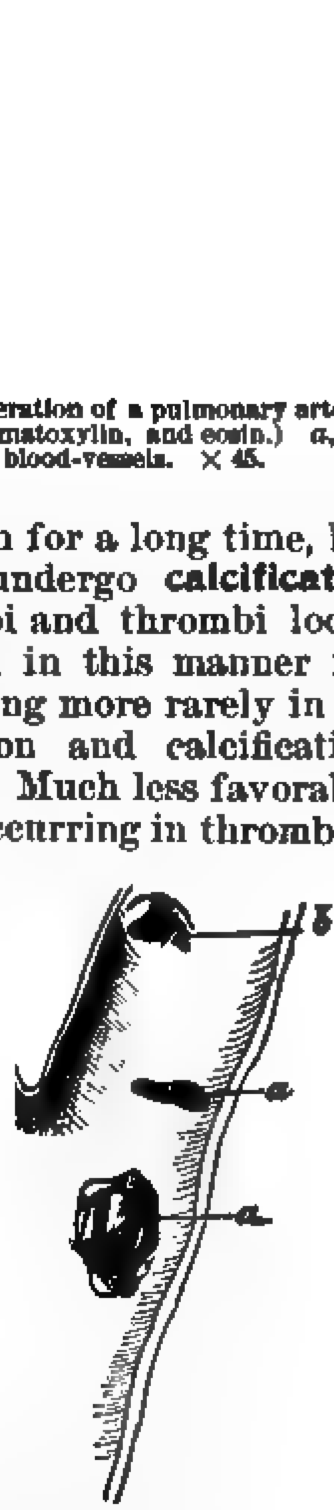

FIG. 25.—Remains of embolic plugs in a branch of the pulmonary artery. *a*, Contracted embolus traversed by connective-tissue threads; *b*, cords of connective-tissue crossing the orifices of branch vessels. (Natural size.)

In the **yellow puriform** or **septic softening** the thrombus breaks down into a yellow, or grayish-yellow, or reddish-yellow, pus-like, grumous, creamy, and at times foul-smelling mass, consisting of pus-corpuscles and a large amount of finely-granular substance, composed of fatty and albuminous detritus and micrococci.

This mass acts as a destructive irritant upon the surrounding tissues, giving rise to inflammation. As a result the intima becomes cloudy, and there arises a purulent inflammation in the media and adventitia, as well as in the tissues about the vessel. After a short time all the vascular coats become infiltrated and present a dirty-yellow or grayish-yellow appearance. A suppurative destruction of the tissues finally results. If puriform masses are transported by the blood-stream to other parts of the vascular system, they will give rise to metastatic foci of necrosis and septic disintegration of the tissues, and purulent inflammation, involving not only the vessel-wall but also the neighboring tissues.

The process of puriform softening of a venous or arterial thrombus, associated with a purulent infiltration of the vessel-wall, is designated **thrombophlebitis purulenta** or **thrombo-arteritis purulenta.** The inflammation of the vessel-wall may take its start either in the softening thrombus or in the tissues adjacent to the vessel. In the latter case the

FIG. 26.—Embolism of an intestinal artery, with suppurative arteritis, embolic aneurism, and periarterial, metastatic abscess. (Alcohol, fuchsin.) *a*, *b*, *c*, *d*, *e*, Layers of the intestinal wall; *f*, artery wall; *g*, embolus, surrounded by pus-corpuscles, lying in the dilated artery which is partly destroyed by suppuration; *h*, parietal thrombus; *i*, periarterial purulent infiltration of the submucosa; *k*, veins gorged with blood. × 27.

softening of the thrombus is coincident with the inflammation of the vessel-wall or else follows it. These processes occur most frequently in the neighborhood of purulent foci.

The most favorable sequela of thrombosis is the **organization of the thrombus**—that is, a **substitution of the thrombus by vascularized connective tissue.**

The new connective tissue develops from the proliferating cells of the vessel-wall, and all the coats of the vessel may take part in the proliferation. The thrombus itself takes no part in the organization; it is a dead mass which excites inflammation in the surrounding tissues. In the course of time the dead thrombus-mass is replaced by vascularized connective tissue (Fig. 24, *b*, *c*, *d*).

The cicatricial tissue formed in the place of the thrombus contracts more or less in the course of time. The cicatrices formed after ligation may thus become very small. Such a cicatrix in the continuity of a vessel may later appear simply as a thickening of the vessel-wall, or there may remain only threads and trabeculæ (Fig. 23, *b*, *c*, *d*), which cross the lumen of the thrombosed vessel, so that the blood-stream can once more pass the affected spot. Not infrequently the connective-tissue strands crossing the vessel cause a marked narrowing of the lumen; or the vessel may become completely obliterated (Fig. 23, *a*), so that the vessel for a greater or less distance becomes converted into a solid fibrous cord.

The pieces broken loose from a thrombus and carried into an artery and there lodged—that is, **emboli**—generally induce new deposits of fibrin upon their surface. Later they undergo the same changes as thrombi, and may either soften, or contract (Fig. 25, *a*), or become calcified. If the emboli are non-infective they usually become replaced by vascular connective tissue (Fig. 24, *b*, *c*).

In many cases the new-formation of connective tissue leads to the obliteration of the artery (Fig. 24). In other cases in the place of the embolus there is developed only a ridge of connective tissue or a nodular or flat thickening of the intima. In still other cases the lumen of the vessel is traversed by strands of connective tissue (Fig. 25, *b*), which either run separately or, interlacing, form a fine- or coarse-meshed network.

If pyogenic organisms are present in the emboli, as is very likely to be the case when the emboli arise from a thrombus lying in a suppurating focus, there is produced a purulent process (Fig. 26, *i*) at the site of the embolus (Fig. 26, *g*), and occasionally ulceration also.

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See also § 38.

§ 40. As **stasis** or **stagnation of the blood** is designated a stoppage of the circulation without coagulation, in which condition the red blood-cells are so closely pressed together that the small vessels appear filled

FIG. 27.—Congestive stasis in the vessels of the corium and papillæ of the plantar surfaces of the toes from a man dying of valvular disease, heart failure, and arteriosclerosis. (Müller's fluid, alum carmine.) Toes presented a deep violet color, and beginning gangrene. × 20.

with a red mass of blood, in which the outlines of the individual red blood-cells cannot be distinguished (Fig. 27). The cause of this condition lies most frequently in the occurrence of a marked *passive congestion.* When the blood entering into a certain tissue-area finds no avenue of exit, the circulation in the small veins and capillaries, and even in the smallest afferent arterial branches, comes to a permanent standstill. Since from the arteries there come with every pulse-wave fresh masses of blood to the congested area, the capillaries and veins become more and more distended and the pressure within these rises to the height of that at the point of divergence of the nearest permeable artery. In this way a large portion of the fluids of the blood are pressed out of the capillaries and veins, and as a result of this the red blood-cells become so closely packed together that their contours are no longer distinguishable, and the total contents of the vessel form a homogeneous, scarlet-red column

(Fig. 27). The red blood-cells, however, are not fused together; as soon as the hindrance to the outflow is removed and the circulation restored, the individual corpuscles become once more separated from one another.

Stasis may be caused by many injurious influences which affect the vessel-wall and the blood itself. Thus, for example, *heat and cold, irritation with acids and alkalies, action of concentrated solutions of sugar and salt, action of chloroform, alcohol, etc.*, cause stasis. These injurious agents act in the first place by abstracting water from the blood and vessel-walls, and further by producing essential changes in the composition of the blood-corpuscles, blood-plasma, and vessel-walls; so that the red cells become less mobile and the vessel-walls come to offer increased frictional resistance to the blood-stream, and at the same time to permit the fluid portions of the blood to pass through them the more readily. Stasis may also be produced by loss of water and drying of the tissues, an event which may occur, for example, in injuries which lay bare tissues lying within the body (intestine).

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IV. Œdema.

§ 41. The free fluid which permeates the tissues is essentially a transudate from the blood, though under certain conditions a portion of the tissue-fluids contained in the cells and fibres may also pass over into the free lymph. The passage of fluid from the vessels is in part a process of filtration and in part is to be regarded as of the nature of a secretion, accomplished by means of a specific function of the capillary walls. The fluid secreted by the capillaries mingles with the products of metabolism in the tissues, and is taken up from the tissue-spaces by means of the lymph-vessels, and through the thoracic duct is again returned to the venous blood.

Every increase in the transudation of the fluids of the blood causes first a more marked saturation of the tissues, which may be compensated for by an increased absorption through the lymph-vessels. This compensation has, however, its limits; with increased transudation from the blood-vessels there is produced a more or less permanent over-saturation of the tissues with the transuded fluids.

The condition which is produced by this collection of fluids in the tissues is known as **dropsy, œdema,** or **hydrops.** According to the extent of the condition there may be distinguished a *general* and a *localized hydrops.* An œdema extending over the superficial portions of the body is known as **anasarca** or **hyposarca.**

The transudate from the blood which constitutes the œdema or the hydrops is always much poorer in albumin than the blood-plasma. The fluid collects at first in the tissue-spaces as *free tissue-fluid* pushing apart the tissue-elements (Fig. 28, *b*), but may also soak *into the tissue-elements* themselves and cause a *swelling* of the cells and fibres, and, under certain conditions, the formation of *vacuoles* (Fig. 29), due to the collection of drops of fluid in the cells or their derivatives.

This may be most frequently demonstrated in the epithelium of the body-surfaces and of glands, but becomes at times distinctly evident in

other tissue elements—for example, in connective-tissue cells and muscle-fibres (Figs. 29 and 30), whose fibrillæ become pushed apart by drops of fluid. Moreover, it often happens in œdematous tissues that cells be-

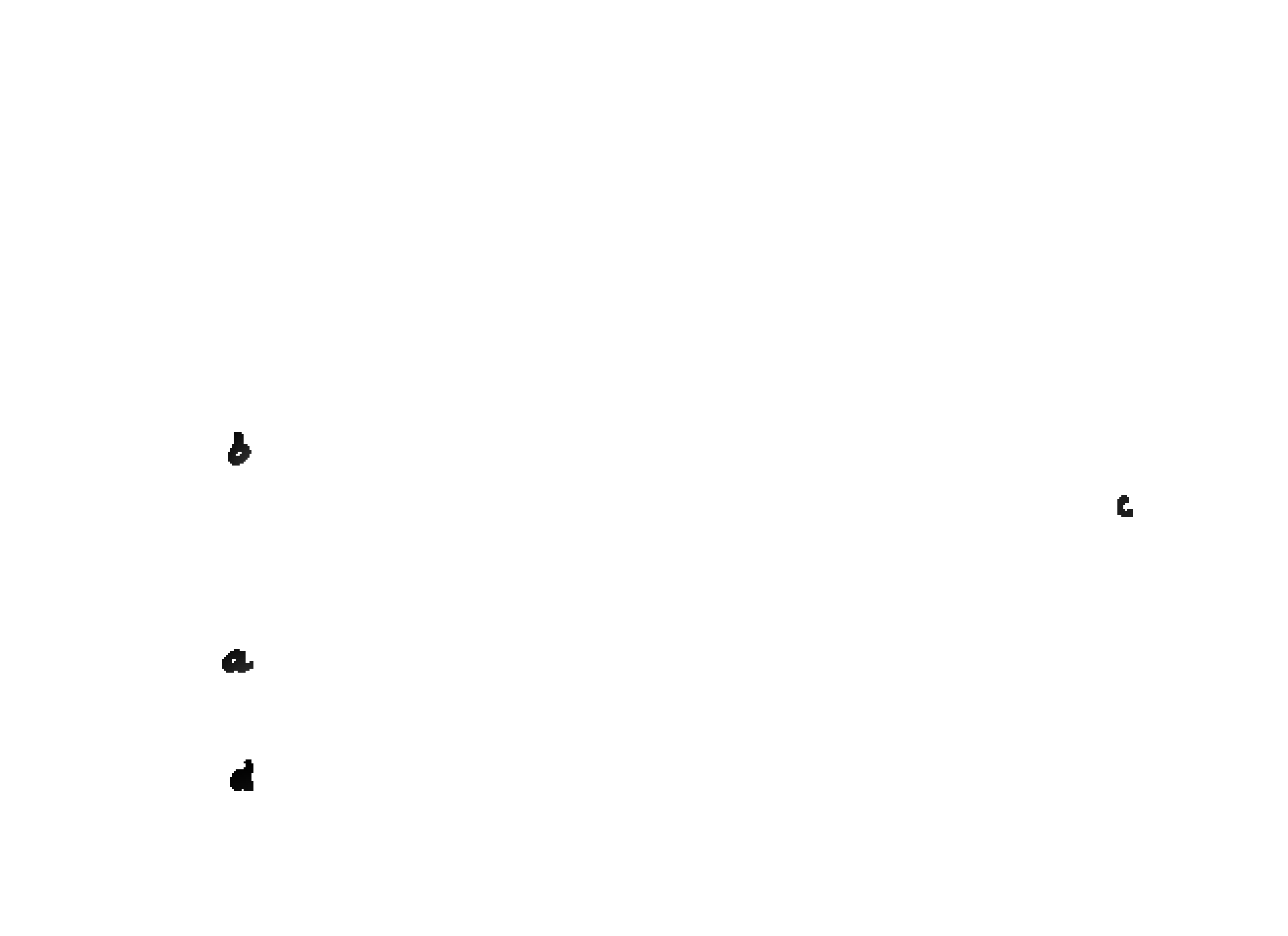
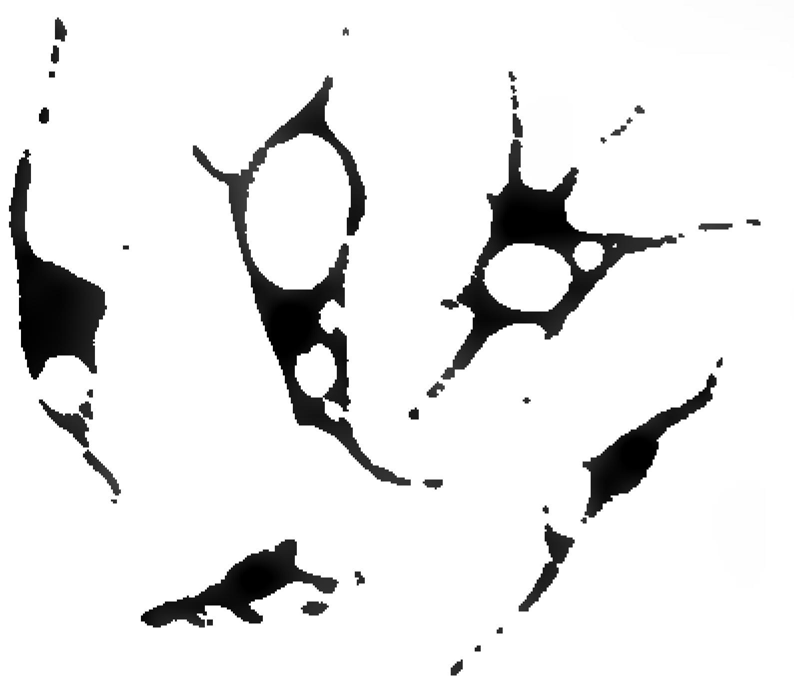


Fig. 30.—Stasis-œdema of the papillary bodies of the skin of the leg from a case of mitral stenosis. [illegible] a, Lymphocytes; b, connective tissue fibrillæ with cells; c, red blood-cells; d, blood-vessel. × 300.

come loosened from their basement-membrane, particularly in the lungs and serous membranes, where the epithelial cells in large number may be mixed with the fluid. In œdema of the skin, the epidermis (Fig. 31) may be separated and lifted up from the papillary bodies, while at the same time the fibrillæ of the latter are pushed apart.



Tissues which are the seat of œdema appear swollen, though the degree of swelling depends essentially upon the structure of the affected tissue. The skin and the subcutaneous tissue are able to take up into their lymph-spaces large quantities of fluid, so that an extremity may become enormously swollen through œdema. In this condition it is pale, possesses a doughy consistence, and pits on pressure. On incision an

abundance of clear fluid escapes, showing the tissues to be thoroughly saturated with fluid.

The lung behaves in a similar way. Owing to its limited space it cannot become greatly distended, but it contains great numbers of cavities filled with air, which, in the advent of œdema, become filled with fluid, which on pressure escapes from the cut surface, generally mingled with air-bubbles.

Œdematous swellings of the kidney, which may become very marked, are caused especially by the retention in the dilated urinary tubules of the water of the urine secreted by the glomeruli. In the connective tissue between the tubules large amounts of fluid collect but rarely.

FIG. 30.—Longitudinal section of œdematous muscle-fibres from the calf muscles in a case of chronic œdema of the legs. (Flemming's solution, safranin.) × 45.

The amount of blood contained in œdematous tissues is variable, and their color varies accordingly.

Body-cavities which are the seat of a dropsical effusion contain at one time a large, at another time only a small amount of a clear, usually light-yellow, rarely quite colorless, alkaline fluid, which at times contains a few fibrin flakes (see the chapter on Inflammation) Compressible organs are compressed by the effusion; the body-cavities are dilated.

FIG. 31.—Inflammatory œdema of the papillary bodies, with elevation of the epidermis from the papillary bodies by an inflammatory exudate, from a case of phlegmon of the thigh. (K. Ziegler, l. c.). *a*, Corium; *b*, exudate consisting of fluid, fibrin and leucocytes. × 40.

A collection of fluid in the abdominal cavity is known as **ascites.**

The albumin-content of pure transudates is not the same in all the body-cavities and tissues, but differs in a pronounced degree. According to Reuss, the albumin-content of transudations of the pleura is 22.5 *pro mille;* that of the pericardium, 18.3; of the peritoneum, 11.1; of the subcutaneous connective-tissue, 5.8; of the cavities of the brain and spinal cord, 1.4. These facts may be taken as a proof of the different constitution of the vessel-walls in the various tissues of the body.

The water of the organs and tissues, according to *Heidenhain* ("Versuche und Fragen zur Lehre von der Lymphbildung," *Arch. f. d. ges. Phys.*, 49 Bd., 1891, and Verh.

des X. internat. med. Cong., ii., Berlin, 1891) consists of three parts—the water of the blood present, the lymph of the organ under consideration, and the water contained in the cells and fibres—the tissue-water. Under certain conditions the last-mentioned may undergo considerable variation, and can increase at the expense of the free water of the blood or lymph, or diminish in their favor.

If the proportion of crystalloid substances (urea, sugar, salts) in the blood be increased, both the blood and lymph become at the same time richer in water; and this is possible only in that the substances injected into the blood pass into the lymphatics, and, by their affinity for the tissue-water, excite a passage of water from the tissue-elements. The rapid passage of the crystalloid substances from the blood into the lymph is accomplished with the aid of a force inherent in the capillary cells, and is not a simple diffusion-phenomenon. This is evident by the fact that the content of the lymph in sugar or salts is often greater than that of the blood.

§ 42. According to their etiology we may distinguish **five varieties of œdema**: œdema due to *arterial congestion;* œdema *from stagnation of the blood;* œdema *caused by a hindrance to the outflow of the lymph;* œdema *caused by disturbance of the capillary secretion* due to changes in the capillary walls; and *œdema ex vacuo.* The fourth one of these varieties is designated by the practising physician as inflammatory, hydræmic or cachectic, or neuropathic œdema, according to the clinical features of the case.

Œdema due to arterial congestion occurs acutely in localized areas, in the skin and subcutaneous tissue, mucous membranes, larynx, bronchi (asthma), nose, periosteum, and muscles (fleeting rheumatic pains), and has usually a *neurotic character.* In individuals showing the tendency in a marked degree, bullæ may even be formed in the skin.

Œdema due to stagnation of the blood arises when, as a result of the marked hindrance to the outflow of blood from the capillaries, the pressure in the capillaries rises and the fluid portion of the blood seeks a lateral outlet, so that an increased amount of fluid escapes from the vessels. The amount of the escaped fluid is the larger the greater the degree of discrepancy between inflow and outflow; it is therefore increased through a coincident increase of the blood inflow.

The escaping fluid is always poor in albumin, but with increased pressure in the veins the albumin-content is increased (Senator); the fluid contains lymphocytes (K. Ziegler) and red blood-cells, the number being increased in proportion to the degree of stagnation.

The immediate result of an increased transudation from the blood-vessels is an increase in the lymph-flow, and this may be sufficient to carry off all the fluid. If it does not so suffice, the fluid collects in the tissue-spaces and there results the condition of stagnation-œdema or dropsy. According to Landerer, this occurrence is favored especially by the fact that the elasticity of the tissues becomes diminished as the result of the long-continued increase of the pressure to which they are subjected. In chronic œdema of long standing the lymphocytes in part undergo progressive changes and are transformed into the cells known as klasmatocytes, plasma-cells, and mast-cells (K. Ziegler).

Obstruction to the outflow of lymph, as experiments in this direction have shown, is not ordinarily followed by œdema. The lymph-vessels in the different regions of the body possess such extensive anastomoses that an obstruction to the outflow of lymph does not readily occur. Even when all of the lymph-channels of an extremity are obstructed, if the amount of lymph formed is normal there results no œdema, inasmuch as the blood-vessels are able to take up the lymph again. Only the *occlusion of the thoracic duct* is likely to lead to a stagnation of the lymph

and the production of œdema, particularly of ascites, but it must be observed that even in this case collateral channels may be opened up and suffice to carry off the lymph.

Although lymphatic obstruction is not ordinarily sufficient in itself to produce œdema, yet it does increase an œdema caused by an increased transudation from the blood-vessels.

Pathological changes in the walls of the capillaries and veins of such a nature as to cause an increase in the vascular secretion, and thereby **give rise to an œdema,** may occur as the result of a *long-continued passive congestion* and the consequent imperfect renewal of the blood. Such changes occur, however, much more frequently as the result of prolonged *ischæmia, lack of oxygen, action of high or low temperatures, traumatic injury,* the *development of tumors* (especially in the serous membranes), *infection,* and *intoxication.* It is also probable that either *irritation or paralysis of the vasomotor nerves* may lead to an increase of the vascular secretion. Just what changes the vessels suffer under these conditions we are not able to state precisely, but it may be assumed that some alteration of the endothelial cells and of the cement-substance plays the chief rôle rendering the vessels more permeable. The œdemas produced by the influences above mentioned may be classed according to their cause as **toxic, infectious, thermal, traumatic, ischæmic, neuropathic,** etc.; and such a classification has much to commend it. Hitherto the forms of œdema here under consideration, with the exception of the neuropathic forms, have been classed ordinarily into two groups—namely, inflammatory and cachectic œdema.

Inflammatory œdema is without doubt to be referred to an alteration of the vessel-wall, and occurs both as an independent affection, in the form of circumscribed or more diffuse swellings and hydropic effusions, and also as a coincident phenomenon in the neighborhood of severe inflammatory processes. In the latter case it is frequently designated *collateral œdema.* Inflammatory œdema is distinguished from stagnation-œdema by the fact that the transuded fluid is markedly *richer in albumin* and *in the number of white blood-corpuscles* present, and, further, in the fact that larger masses of coagula (Fig. 31, *b*) occur in it (see chapter on Inflammation). Its cause is to be sought sometimes in infectious and toxic, sometimes in thermal and traumatic influences, at other times in a temporary ischæmia.

As to **hydræmic** or **cachectic œdema,** it was formerly believed that hydræmia—that is, the diminution of the solid elements of the blood—as well as hydræmic plethora—that is, a retention of water in the blood—could directly cause an increased transudation from the blood-vessels. It was supposed that the vessel-walls behaved as dead animal membranes, and allowed a fluid poor in albumin to filter through more easily than one richer in albumin. The vessel-wall is not, however, a lifeless animal membrane, but must be regarded as a living organ. A hydræmia experimentally produced does not, according to Cohnheim, give rise to an œdema. Even when a hydræmic plethora is produced by the over-filling of the blood-vessels with a watered blood, and there results an increased transudation from the vessels, eventually leading to œdema, the œdema so produced occurs only when the proportion of water in the blood becomes very high, and does not develop in the same regions where the so-called hydræmic œdema in man appears. We must therefore assume that the œdema of cachectic individuals, as well as that occurring in individuals suffering from nephritis with impairment of renal func-

tion, depends essentially upon an *alteration of the vessel-wall*, which is caused either by the hydræmic character of the blood or by a poison circulating in the blood. Probably other lesions of the tissue through which the elasticity of the latter is diminished are also concerned. *Hydræmia* therefore *favors the occurrence of œdema*, but is not the sole cause thereof, and, in particular, does not determine its localization.

Cachectic œdema is in part allied to stagnation-œdema and in part to inflammatory œdema, in that at one time the circulatory disturbance is a prominent feature, at another time the vascular alteration.

Œdema ex vacuo occurs chiefly in the cranial cavity and in the spinal cord, and arises in all cases in which a portion of the brain or spinal cord is lost and not replaced by some other tissue. In atrophy of the brain and spinal cord the subarachnoidal spaces in particular become enlarged, occasionally the ventricles also. The fluid has the same albumin content as the normal cerebrospinal fluid. Local defects become filled either by a dilatation of the nearest subarachnoidal spaces or of the adjacent portions of the ventricles, or through a collection of fluid at the site of the defect itself.

According to *Cohnheim* and *Lichtheim*, injections of aqueous solutions of salt into the vascular system of dogs (*Virch. Arch.*, 69 Bd.) show that hydræmia does not produce œdema. If the mass of the fluids of the blood be increased, there results an increase of almost all the secretions (saliva, intestinal juices, bile, urine, etc.), and also of the flow of the lymph; the latter, however, not universally, in particular not in the extremities. In a high degree of hydræmic plethora the abdominal organs become dropsical, but never the extremities. Control-experiments recently carried out by *Francotte* confirm the observation that hydræmic plethora artificially produced in animals causes in the first place a dropsy of the abdominal organs; but this observer was able to produce also an œdema of the skin and subcutaneous tissues.

The view that the so-called hydræmic œdema is merely the result of an increase in the absolute amount of water in the blood, is championed especially by *von Recklinghausen* and by *Pisenti*. The distribution of the dropsy is, according to *von Recklinghausen*, essentially dependent upon bodily position, external pressure, impeded circulation, difference in the innervation of different vascular areas, and the consequent difference in the fulness of their vessels.

I can subscribe to these opinions only in so far as they apply to the influence of the above-mentioned modifying factors upon the distribution of the œdema, but not as regards the main point. For the other side speak not only the experiments of Cohnheim and Lichtheim above mentioned, but also the fact that in nephritic and cachectic individuals œdema not infrequently appears at a time when no hydræmic plethora is present; and, further, in cases of hydræmic plethora no œdema may occur. I therefore look upon the increase in the amount of water as only one factor which is favorable to the occurrence of œdema.

According to the investigations of *Pickhardt*, pathological transudates constantly contain uric acid: the fluid of ascites about 0.0036 per cent; the fluid of œdema, 0.0075 per cent; and pleuritic exudates about 0.0015 per cent. Sugar is also constantly present, usually as dextrose.

Effusions into the large serous cavities of the body occasionally present a *milky appearance*, or a certain degree of opalescence. This phenomenon is most often due to the presence of chyle (*hydrops chylosus*), or of fat (*hydrops adiposus* or *chyliformis*), or of both. Moreover, the presence of different albuminoid bodies, mucoid substances (*Hammarsten*), casein-like bodies (*Lion*), lecithin (*Mitchell, Mattiroli, Gross*), may produce cloudiness of the transudate. In so far as chyle is not the cause, the substances producing the cloudiness arise for the greater part from disintegrating cells. According to *Bernert*, a cloudiness may be produced by albumins belonging to the group of globulins, from which by means of hot alcohol considerable amounts of lecithin may be obtained. The fat-content is, moreover, very low.

According to *Heidenhain*, the specific function of the capillary walls plays a controlling part in the formation of the lymph. Consequently, the lymph-production can be influenced by various substances present in the blood. The crystalloid substances are quickly eliminated from the capillaries, and cause a discharge of tissue-fluid into the lymph, as has already been mentioned in § 41. *Heidenhain* has, however, found substances which, when injected, cause an increase in the transudation of water from

the blood into the lymph. This may be accomplished, for example, with decoctions of the muscles of crabs and of fresh-water mussels, or of the heads and bodies of leeches, or through injections of peptone and egg-albumin. By these means the amount of lymph flowing from the thoracic duct may be increased five-, six-, and fifteenfold. At the same time the amount of organic constituents in the lymph is increased. The active substances must therefore stimulate the specific function of the cells of the vessel-walls which secrete the lymph. According to these observations, it is probable that many of the affections of the skin described as neuropathic, and which are characterized by hyperæmia associated with œdematous swelling—as, for example, urticaria, erythema nodosum, herpes zoster—are to be regarded as symptoms of intoxications coupled with nervous affections and with disturbance of the secretory activity of the capillaries. It is also possible that the secretion of the capillaries may be directly affected by nervous influences.

Magnus, on the other hand, on the ground of experimental investigation (infusions of physiological salt-solutions in normal animals, irrigation of dead animals with salt-solution after poisoning with arsenic, chloroform, chloral hydrate, and ether, and after the removal of the kidneys and ligation of the ureters), arrives at the following conclusions: The capillary walls during life offer a resistance to the passage of fluids; after death this resistance disappears. An injury to the capillary wall, and a diminution of its resistance, favor the occurrence of œdema. There are poisons which are able to injure the capillary wall in such a manner that it becomes abnormally permeable.

Albu emphasizes likewise the importance of the increased permeability in the case of the escape of a large amount of blood-serum. Hydræmia and plethora may constitute the conditions favoring this.

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See also § 46.

V. Hæmorrhage and the Formation of Infarcts.

§ 43. By **hæmorrhage** is understood the escape of all the constituents of the blood from the vessels (*extravasation*) into the tissues or upon a free surface. It may be either *arterial*, *venous*, or *capillary*, or the blood may escape from the *heart*. The blood which has escaped from the vascular system is termed an **extravasate.** For the designation of especial forms of hæmorrhage a very great variety of terms is used. If the hæmorrhagic foci are small, and form more or less sharply outlined, punctate, red or dark-red spots, they are called *petechiæ* or *ecchymoses*; if they are larger and not sharply outlined, they are known as *suggillations* and as *bloody suffusions*. If the affected tissue is firmly infiltrated with the escaped blood, but not torn or destroyed, the condition is spoken of as a *hæmorrhagic infarct*. If the extravasated blood forms a large mass, this is known as a *hæmatoma* or *blood-tumor*.

The blood which escapes from the vessels into the tissues collects at first in the tissue spaces (Fig. 32). Large hæmorhages may completely conceal the structure of the tissue (Fig. 33, *d*). Delicate tissues, as those of the brain or spinal cord, may be destroyed by large hæmorrhages.

If the hæmorrhage occurs on the free surface of an organ, the blood either escapes externally or is poured into a neighboring cavity.

Hæmorrhage from the nose is called *epistaxis*; vomiting of blood, *hæmatemesis*; bleeding from the lungs, *hæmoptoë* or *hæmoptysis*; from the uterus, *metrorrhagia* and *menorrhagia* (during the menses); hæmorrhage from the urinary organs, *hæmaturia*; hemorrhage from the sweat-glands, *hæmatidrosis*.

A collection of blood in the uterine cavity is designated as *hæmatometra*, in the pleural cavity as *hæmothorax*, in the tunics of the testicle as *hæmatocele*, in the pericardium as *hæmopericardium*.

Hæmorrhages of the skin not caused by trauma are usually termed *purpura* (Fig. 32). Collections of blood and fluid beneath the epidermis in the place of the dissolved deeper epithelial layers give rise to *hæmorrhagic blebs*.

FIG. 32.—Hæmorrhage in the skin near the knee; from a man eighty-one years of age. (Formalin, hæmatoxylin, and eosin.) × 80.

Recent extravasations show the characteristic color of either arterial or venous blood. Later the extravasate shows various alterations which are characterized particularly by color-changes. Suggillations of the skin become first brown, then blue, and green, and finally yellow. In the course of time the extravasate is absorbed (see Chapter V.), and during this absorption tissue-proliferation often occurs. Large collections of blood may become partly organized into connective tissue or may become encapsulated (see Chapter VII.).

A **hæmorrhage** may occur, in the first place, from **rupture of the heart** or the **vessel-wall**—that is, **per rhexin** or **per diabrosin.** This is the only form of cardiac and arterial hæmorrhage. From the capillaries and veins hæmorrhage may occur also **per diapedesin**—that is, by a process in which the red cells escape through the vessel-wall without the occurrence of a tear in the same. Very often such hæmorrhages are small and of slight extent; in other cases the process continues for a longer time, and the infiltration of the tissues with red cells reaches a significant degree. Hæmorrhages by diapedesis are therefore not always small, hæmorrhages by rhexis not always large. The rupture of a capillary or small vein does not give rise to a large hæmorrhage; on the other hand, a hæmorrhage through diapedesis can reach an important size.

The **causes of interruption of continuity of the heart-wall and vessel-walls** are in part *traumatic injuries*, in part *increase of intravascular pressure*, and in part *diseased conditions of the heart and vessel-wall*. Increase of the blood-pressure in the capillaries and smallest veins can lead to rupture without the aid of vascular changes, particularly in the case of marked passive congestion. The heart, normal arteries, and normal veins of large size cannot be ruptured through increase of pressure alone, but abnormally thin-walled or diseased areas in either the heart,

arteries, or veins may be so ruptured. Newly formed vessels are easily torn.

Diapedesis may be caused by an *increase of pressure* in the capillaries and veins, as well as by an *increased permeability of the vessel-wall.* If the outflow of the venous blood in a given vascular area be ob-

FIG. 33.—Traumatic cerebral hemorrhage. (Formalin, hæmatoxylin, and eosin.) *a*, Normal brain substance; *b*, blood-vessel; *c*, perivascular collection of blood; *d*, larger area of hemorrhage with destruction of the brain substance. × 100.

structed, diapedesis of red cells from the capillaries and veins takes place; and this is to be regarded as a result of the increased pressure in the vessels. Diapedesis as a result of changes in the vessel-wall occurs particularly after mechanical, chemical, and thermal lesions of the vessel; and it may be assumed that certain *poisons* produce especially marked changes in the vessel-walls. Further, an abnormal permeability of the vessel-walls is also observed when for a long period the vessels have not been traversed by the blood-stream, and have suffered in their nutrition in consequence.

When an individual shows a special tendency to hæmorrhage, the condition is designated as **hæmorrhagic diathesis.** Two forms may be distinguished—a congenital and an acquired.

The **congenital hæmorrhagic diathesis** or **congenital hæmophilia,** which, as already mentioned in §§ 15 and 16, belongs to the diseases which may be inherited, depends most probably upon an abnormal constitution of the vessel-walls. The composition of the blood may also be pathological, so that a hæmorrhage once started is not arrested, as usual, by the coagulation of the blood.

An **acquired hæmorrhagic diathesis** occurs, in the first place, in those diseases which are known as scurvy, morbus maculosus Werlhofii, purpura simplex, purpura (peliosis) rheumatica, purpura hæmorrhagica, hæmophilia, and melæna neonatorum (gastric and intestinal hæmorrhages), and Möller's or Barlow's disease; and, further, in many infec-

tions and intoxications—namely, septicæmia, endocarditis, anthrax, typhus fever, cholera, smallpox, plague, acute yellow atrophy of the liver, yellow fever, nephritis, phosphorus poisoning, after snake-bites, etc.; and, finally, also in pernicious anæmia, leukæmia, and pseudoleukæmia. In the first group of diseases named—all of which are characterized by hæmorrhages in the skin, mucous membranes, and parenchyma of various organs and tissues (in Barlow's disease, which often occurs in children of from one and one-half to two years old in association with rickets, the hæmorrhages are subperiosteal)—the cause has been generally supposed to lie in *disturbances of nutrition and of the circulation;* but recent observations make it very probable that these affections, at least in a great part, belong to the *infectious diseases.* W. Koch is of the opinion that scurvy is an infectious disease, and that the different forms of purpura, erythema nodosum, and the hæmorrhages occurring in the new-born represent varieties of this infection. In the last few years bacteria have been repeatedly found in these conditions—namely, purpura hæmorrhagica and the hæmophilia of the new-born. In this connection should be mentioned especially the investigations of Kolb, Babes, Gärtner, Carrière, Tizzoni, and Giovannini, who have found in these diseases certain bacilli which were pathogenic for animals, and which, when inoculated into the latter, produced a disease characterized by hæmorrhages. These diseases are also associated with other infections characterized by hæmorrhages, and it may be assumed that the hæmorrhages are in part caused by *local changes of the vessel-wall* which are due to *local development of bacteria,* and in part *to the injurious influence of the toxic substances produced by the bacteria themselves.*

The hæmorrhages occurring in anæmic conditions are to be regarded as the result of *anæmic degeneration of the vessel-wall,* though partly also as a result of *circulatory disturbances.*

A number of apparently spontaneous hæmorrhages are connected with *irritation or paralysis of the vasomotor nerves,* arising either from the central nervous system or by reflex action, or through lesions of the conducting nerve-fibres. In this category belong the hæmorrhage of menstruation, many forms of hæmorrhage from the nose, intestine, and urinary bladder, also hæmorrhages from the conjunctiva, skin (stigmatization), from the normal kidney, mammary glands, from hæmorrhoids, wounds, etc. Further, certain hæmorrhages from the lungs following severe cerebral lesions are also to be considered in this connection, though in a given case it is not always possible to judge with certainty, since disturbances of respiration, as well as the aspiration of irritating substances into the lungs, may likewise lead to hyperæmia and to hæmorrhages in the lung. Finally, in cerebral disease, particularly in disease of the crura cerebri, there occur hæmorrhages from the stomach and intestines, which are dependent upon the cerebral lesion.

Hæmorrhages per rhexin cease when the extravascular pressure comes to equal the pressure within the bleeding vessel, or when the narrowing of the vessel and the processes of coagulation and thrombosis close the rent. *Hæmorrhage by diapedesis ceases* through a cessation of blood-supply to the bleeding vessel, or when the abnormal intravascular pressure is lowered and the vessel-wall is restored to its normal state.

The process of diapedesis may be observed under the microscope in the frog's mesentery or web. If before the examination the efferent veins are ligated, the capillaries and veins are seen to be engorged with blood. After a certain time the red

blood cells begin to pass from the capillaries and veins (see *Cohnheim*, "Allgem. Path.,' *l.*, and *Virch. Arch.*, 41 Bd.). *Arnold* (*Virch. Arch.*, 58, 62 u. 64 Bd.) believed at first that at the place of exit of the corpuscular elements spaces between the endothelial cells must exist, and these he designated as stigmata and stomata; later he found that the supposed openings consisted of more marked heaping-up of the cement-substance between the endothelial cells. Under pathological conditions the cement-substance gives way and allows the red blood-cells to pass through.

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§ 44. The **sudden closure of an artery** by thrombosis, or embolism, or by ligation, or by any other means, leads, as has already been stated (§ 39), to a stoppage of the circulation beyond the point of obstruction, after the vessel has more or less completely emptied itself by the contraction of its walls. At the same time there is an increase of pressure in the vessel from the point of obstruction back to the point of divergence of the nearest arterial branch. If the branches of the artery beyond the point of obstruction have free arterial communication with some other unobstructed artery, the latter by becoming dilated may be able to supply a sufficient amount of blood to the affected area and the circulation is thus restored.

If the area of the obstructed artery has no collateral connections through which it may draw its blood-supply, the portion of tissue deprived of blood remains anæmic and dies, thus giving rise to an **anæmic infarct**. Parenchymatous organs—as, for example, the spleen and the kidneys—present in such infarcted areas a cloudy, opaque, yellowish-white, often clay-colored appearance. (See § 48.)

When the area of distribution of the obstructed vessel possesses no collateral anastomoses, as in the case of a **terminal artery**, but if, on the other hand, there is a scanty influx of blood from neighboring capillaries or from the veins, a **hæmorrhagic infarct** may be formed. The capillaries of the area rendered anæmic by the obstruction become gradually filled once more with blood, which in part comes from the capillaries of the adjacent vascular area, and in part from the veins, from which the blood flows in a retrograde direction. The blood flowing in from the adjacent capillaries is under very low pressure, which is not sufficient to drive the blood quickly through the obstructed area into the veins. When the conditions of pressure become such that a retrograde current sets in from the veins into the capillaries, the restoration of the normal circulation becomes wholly impossible.

The imperfect circulation in the obstructed area, which, through processes of coagulation in the veins and capillaries, is finally brought to a complete standstill, leads, in case there is not a restoration of the normal flow of blood in the vascular system through a speedy adjustment of pressure, sooner or later to a degeneration and necrosis of the vessel-wall, and thereby to an increased permeability of the same. As a result, if the afflux of blood be continued, there occur in the stagnated area a *diapedesis of red cells* and an infiltration of the tissue with extravasated blood-corpuscles, through which the obstructed area acquires a dark-red color and a firmer consistency; a *hæmorrhagic infarct* is thus formed (Fig. 34).

Embolic hæmorrhagic infarcts occur in the lungs (Fig. 34), but are formed after the embolic obstruction of an artery *only when there exists a passive congestion of the lungs;* while in the case of a normal pulmonary circulation the disturbances of circulation produced by the embolism are quickly compensated. In the systemic circulation extensive embolic hæmorrhages are confined almost entirely to the region of distribution

FIG. 34.—Hæmorrhagic infarct of the lung. (Hæmatoxylin and eosin.) Alveoli filled with blood: scattered pale nuclei in the alveolar septa and in the blood of the alveolar spaces, belonging partly to connective-tissue cells and partly to leucocytes. × 40.

of the superior mesenteric artery, whose branches, though not terminal arteries, possess but few anastomoses. *Anæmic infarcts* occur especially in the *spleen, heart,* and *kidneys.* Around the periphery of the anæmic area there is always more or less hæmorrhage, so that the pale area of the infarct is surrounded by a *hæmorrhagic border* or at least by *hæmorrhagic spots.* In the case of obstruction of the cerebral arteries or those of the extremities, or the central artery of the retina punctate hæmorrhages may also occur. Within the infarcted area the tissues are wholly or for the greater part dead, and the specific elements of the organ in particular (Fig. 36, *c, d*) die quickly. After a time an exudative inflammation arises in the neighborhood of anæmic and hæmorrhagic infarcts, with the formation of a cellular (Fig. 36, *f*) or a cellular and fibrinous exudate; and this is followed by tissue-proliferation through which the dead, hæmorrhagic area is gradually absorbed and replaced by connective tissue (see Part II. of Chapter VII.).

Virchow, who was the first to carry out extensive experimental investigations with reference to thrombosis and embolism, leaves in his published works the question of the origin of embolic hæmorrhagic infarcts still open; but expresses the opinion that most probably the vessel-walls in the obstructed area suffer changes by which they become more permeable and fragile. If a collateral circulation be afterward established, secondary hæmorrhage, exudation, and extravasation take place as the result of the changes in the vessel-wall. *Cohnheim,* who studied the results of embolism in the frog's tongue directly under the microscope, demonstrated the retrograde flow of blood in the veins, the refilling of the capillaries, and the escape of blood by diapedesis. The cause of the diapedesis he believed to be essentially the disorganization of the

vessel-wall caused by the anæmia. *Litten* regarded the retrograde flow of blood from the veins as unessential, and referred the refilling of the anæmic area to an influx of blood from the capillaries of the neighboring vascular areas. He also regarded the disorganization of the vessel-walls as unnecessary for the production of infarction, inasmuch as the stagnation is sufficient in itself, as in the case of venous obstruction, to explain the diapedesis. The diapedesis is therefore increased whenever in such foci the blood coagulates in the efferent veins. *Von Recklinghausen* considers the principal factor in the formation of a hæmorrhagic infarct to be a hyaline thrombosis of the capillaries of the obstructed area. If blood subsequently enters from neighboring vessels into the still pervious vessels of the area, it encounters resistance, becomes stagnant, and then escapes from the vessels.

The essential cause of the escape of blood in the case of hæmorrhagic infarction lies in the stagnation of the blood in the affected area, and in the degeneration or death of the tissue and the blood-vessel walls. The latter change may be recognized with certainty through the disappearance of the nuclei. Secondary thrombosis in the vessels of the obstructed area is of frequent occurrence, and increases the stagnation and hæmorrhage, but thrombi are not always present at the time of the hæmorrhage, and, therefore, cannot be regarded as the essential factor in the production of the latter.

According to investigations by *Orth*, hæmorrhagic infarcts may be produced in dogs through the introduction of chemically irritating emboli into the pulmonary arteries.

In the lungs, in conditions of passive congestion and inflammation, there not infrequently occur extensive hæmorrhages, which, in case they are restricted to a circumscribed area, closely resemble embolic infarcts. They are usually less sharply outlined and less firm, so that in the majority of cases they are easily distinguished from the embolic infarcts.

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VI. Lymphorrhagia.

§ 45. **Lymphorrhagia** occurs when the continuity of a lymph-vessel is interrupted at any point and the lymph is poured out into the neighboring tissue. Since the pressure in the lymph-vessels is very low—that is, not greater than in the surrounding tissues—an outflow of lymph

from a lymph-vessel can occur only when the injured vessel lies on the external surface, or when a natural cavity is at hand into which the lymph can flow, or when, through the same cause producing the rupture, an open space is formed at the same time in the tissues. So, for example, an escape of lymph together with the blood may take place from wounds, but the outflow is stopped by very slight counterpressure. If, after the wounding of a lymphatic, the opening persists, so that there is a permanent outflow of lymph, escaping externally (as in ulcers) or into one of the body-cavities, there is formed a **lymph-fistula**, through which considerable quantities of lymph may be lost. Most important and also most dangerous is the *rupture of the thoracic duct*, which occurs sometimes as the result of traumatism, and occasionally as a result of an obstruction to the lymph-flow at some point in the lumen of the duct (after inflammation or in the course of the growth of tumors). The lymph is poured out into the thoracic or abdominal cavity, giving rise to a *chylous hydrothorax* or a *chylous ascites*, or in very rare cases to a *chylopericardium*.

In very rare cases it happens that the urine, as it comes from the bladder, has the appearance of a milk-white, or a yellowish, or, through the admixture of blood, a reddish emulsion; and contains besides albumin a large quantity of finely-divided fat-droplets. This phenomenon is known as **chyluria**. It occurs as an endemic disease in certain tropical regions (Brazil, India, the Antilles, Zanzibar, Egypt) where it is caused by a parasite, the *Filaria Bancrofti*, which inhabits the lymph-vessels of the abdominal cavity and there produces its embryos (*Filaria sanguinis*); these, during the repose of the patient in a horizontal position, swarm in great numbers in the blood, and are also found in the chylous urine. The connection between the chyluria and the invasion of the lymph-vessels has not yet been satisfactorily demonstrated by anatomical investigations; but it is probable that the chyle-like fluid does not come from the blood and through the kidneys; but, as a result of the obstruction in the lymph-circulation, chyle escapes from ruptured lymphatics of the bladder and mingles with the urine (*Scheube, Grimm*). In corroboration of this view is the fact that, at autopsy, the abdominal lymphatics exhibit marked dilatation (*Havelburg*), while the kidneys are but little changed; and further, according to an observation made by *Havelburg*, the urine obtained from the ureter showed no admixture of chyle, though chyluria was present at the same time.

The anatomical cause of the non-parasitic chyluria is still unknown.

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See also § 42.

CHAPTER V.

Retrograde Disturbances of Nutrition and Infiltrations of the Tissues.

I. General Considerations Concerning the Retrograde Disturbances of Nutrition and the Tissue-Infiltrations.

§ 46. The **retrograde disturbances of nutrition** are characterized in general by *degeneration* of the affected tissue, often also by *diminution in size* and *disappearance of the individual tissue-elements*, the *functional capacity* of the tissue being, at the same time, *lowered.*

The **tissue-infiltrations** are characterized essentially by the *deposit in the tissue of pathological substances* which have either been formed within the body or introduced into it from without. The *functional capacity* of the part affected is likewise usually *diminished.* The *infiltration is often only a result of preceding degenerative changes,* or may itself *constitute the chief feature of the degeneration.*

Retrograde disturbances of nutrition may affect the body in its fully developed state, or during its period of development and growth; and in either case may lead to an abnormal smallness of the affected organ or tissue. In the former case the diminution in size is due to a disappearance of the individual elements of the affected tissue, and is designated **atrophy.** In the latter case, on the other hand, it is due to a defective development of the affected organ, as shown by a more or less rudimentary condition of its elements. If in this way an organ or a part of an organ wholly fails of development, so that it is totally absent or at least is represented only by its rudimentary anlage, the condition is designated **agenesia** or **aplasia.** But if the development of the affected part is of a certain degree, yet not reaching the normal, the condition is known as **hypoplasia.**

The **causes of agenesia and hypoplasia** are partly intrinsic, and partly extrinsic—that is, the stunting and imperfect development of an organ may depend as well upon a pathological condition of its anlage, as upon external injurious influences which may affect the developing part. The disturbance of development may further affect either the whole body or only a part of the same. In the first case there results a *dwarf;* in the second, a *stunting of individual parts or organs.*

The **causes of the tissue-degenerations and the associated atrophy** are for the greater part to be found in extrinsic harmful influences to which the tissues are exposed during life; but atrophy may also depend upon intrinsic conditions. This latter is particularly the case when the tissues in old age reach their physiological limit and gradually become incapable of properly nourishing and preserving themselves. In many tissues a similar retrograde change, due to intrinsic causes, occurs earlier in life, as, for example, physiologically in the ovary and thymus.

As extrinsic harmful influences which may lead to degenerations

should be considered all those agencies mentioned in Chapter I. Disturbances of circulation, lack of oxygen and food supply, and intoxications play a very important rôle. *In the majority of cases degenerations are localized*, so that we may speak of **degenerations of special tissues** or of **special organs.** Not infrequently the **disturbances of nutrition are more general,** so that the entire organism suffers. Thus the picture of a general disease may be produced by a degenerative or atrophic condition of the blood—that is, a diminution in the number of red blood-cells (oligocythæmia), at times also a deficiency of hæmoglobin (chlorosis), so that a permanent condition of **insufficient blood-supply** or a **general anæmia** is produced, the nutrition of the body being correspondingly impaired.

As the result of a diminished ingestion of food, or of disturbed metabolism, and of an increased waste of the proteids and fats of the body, there may result a condition of general emaciation and weakness, often associated with anæmia, a wasting of the entire body, which is designated **cachexia** or **marasmus.** If under such circumstances it appears likely that certain substances are formed in the body, which, when taken up into the blood and tissue juices, cause a contamination or alteration of these, the condition may be spoken of as a **dyscrasia.**

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II. Death of the Organism.

§ 47. All life comes sooner or later to an end—to **death.** When this occurs at an advanced age, without preceding well-defined symptoms of disease, it may be regarded as a normal termination of life. This occurrence may be attributed, at least in part, to the fact that the functions of certain organs necessary to the maintenance of life, become discontinued as the result of intrinsic causes; although in most cases it is impossible to exclude the action of extrinsic influences in helping to bring about the cessation of function of the organs in question.

When death occurs prematurely—that is, at an age earlier than the average age of death in man—and when preceded by symptoms of disease, it must be regarded as a pathological phenomenon. Its occurrence under these circumstances is for the most part referable to demonstrable extrinsic influences, but at times may be dependent also upon intrinsic inherited causes. It is obviously impossible to draw any sharp line of separation between physiological and pathological death.

The causes of premature—that is, pathological—death are to be found in those influences, which have been discussed in Chapters I. and II. as the causes of disease.

An individual is to be regarded as dead when all of his functions have forever ceased. Death is inevitable at that instant in which one or more of the functions imperatively necessary to life has ceased, though it is not necessary that at that moment all the functions should have ceased. Indeed, it often happens, that after life is irretrievably lost, many organs are still capable of performing their function, and it is only after a certain time that all the organs die. *The life of the organism passes gradually, by progressive cessation of the functions of its different organs, into the state of death.*

Cessation of the functions of the heart, lungs, and nervous system results in an immediate death of the entire organism. Cessation of the functions of the intestines, liver, or kidneys leads inevitably to death after a certain length of time, often measured by days. Destruction of the sexual glands does not endanger the life or health of the affected individual, and likewise man may also spare one or more of his organs of special sense.

The occurrence of death is usually determined by the last recognizable efforts at respiration and by the stoppage of the heart. With the cessation of respiration it is impossible for any organ to remain alive after a certain short period. The stoppage of the heart likewise makes impossible any further nourishment of the tissues, in consequence of which the central nervous system very quickly becomes unable to continue its functions.

After death the body may present a variety of appearances. The aspect of the external visible portions is largely dependent upon the distribution of the blood at the time of death. An abundant supply of blood in the skin gives it a blue-red color, anæmia gives it a pale color. Further, the preceding disease may alter the external appearance of the body in different ways.

Within a certain time after death various changes occur in the tissues of the body, which in part may be regarded as the **absolute signs of death.** In the first place the *temperature of the body falls*, sometimes rapidly, at other times slowly, until it reaches the temperature of the surrounding air. It must be borne in mind, however, that the temperature at times does not begin to sink immediately after death, but first rises somewhat. The rate of cooling of the body depends partly upon the character of the body itself, and partly upon the nature of its surroundings. The time required may vary from one to twenty-four hours.

The *coldness of the dead body* is termed *algor mortis.*

At the time of death the skin for the greater part becomes pale; but after six to twelve hours, sometimes earlier, bluish-red spots appear on the skin over the dependent parts of the body. These are known as the *death-spots* or *livores mortis* (*post-mortem hypostasis*), and are due to the local accumulation of blood in the veins and capillaries of the more dependent portions. They are not found in those parts of the body subjected to the pressure of the weight of the body. Their number and size depend upon the amount of blood in the skin at the time of death. Parts which have been cyanotic during life may retain this appearance after death, especially the head, fingers, and toes. The color of post-mortem hypostasis is usually blue-red; the intensity of the color varies; in cases of poisoning with carbon monoxide it is a bright red.

The weight of the body causes flattening of those muscular parts upon which it rests.

Sooner or later there occurs a stiffening and contraction of the muscles, due to the coagulation of the contractile substance (*Bruecke, Kühne*). This is known as the *cadaveric stiffening* or *rigor mortis.* It usually comes on about four to twelve hours after death, but may occur almost immediately or as late as twelve to twenty-four hours. It begins usually in the muscles of the jaw, throat, and neck, and extends from them to the trunk and extremities. After twenty-four to forty-eight hours it usually vanishes, but under certain conditions may persist for several days.

Rigor mortis affects also the smooth muscle fibres; and the contraction of these in the skin gives rise to the so-called goose-flesh of the cadaver.

The *decomposition of the cadaver* begins with the disappearance of the rigor mortis. Its occurrence is shown partly by the odor of putrefaction, partly by changes of color in the skin and mucous membranes, and through changes in the consistence of the

tissues. The commencement and progress of putrefaction depend partly upon the condition of the body-nutrition and the nature of the disease preceding death, partly upon the conditions of the surroundings, especially the temperature. Not infrequently putrefaction may occur in local dead areas of the body, even before death of the body as a whole. When putrefactive bacteria are present in the body, decomposition of the cadaver may begin immediately after death.

As an early sign of decompositon there is usually present a greenish discoloration of the skin, appearing first over the abdomen. With the progress of putrefaction the unpleasant odor and discoloration increase; and gases are formed in the intestine, later in the blood and in the tissues, which at the same time become soft and friable.

Shortly after death the *cornea becomes lustreless and cloudy, the eyeball loses its prominence*, and *dark spots appear in the sclera*, which, gradually increasing in size, become confluent. These changes are due to evaporation and decomposition. If the eyelids are not closed, the *uncovered portions of the eyeball show the results of drying.* Whenever the skin has lost its epidermis the exposed tissues undergo desiccation.

If all of the phenomena of life be reduced to a minimum, there may result a condition of **apparent death** which may be mistaken for real death. Though post-mortem hypostasis, rigor mortis, and putrefaction are unmistakable evidences of death, these changes may not take place until some time after death, so that an interval is left during which it may under certain conditions be doubtful as to whether death has actually occurred. To ascertain the true condition under such circumstances it must be determined by appropriate examination whether the heart still beats, whether respiration still takes place, whether the blood still circulates, and whether the nerves and muscles retain their irritability.

Conditions which are designated as apparent death occur under a variety of circumstances, as, for example, in individuals suffering from cholera, in cases of catalepsy, hysteria, after excessive bodily exertion, violent concussion of the central nervous system, after severe hæmorrhage, suspension of respiration through hanging, strangulation, or drowning, in certain cases of poisoning, after lightning-stroke, after prolonged exposure to cold, etc. The duration of this condition is usually only short, but may occasionally be extended over several hours or even days.

According to the investigations of *Fuchs* ("Ueber Todtenstarre," *Zeitschr. f. Heilkunde*, 1900), the *heart* is the first muscle to show rigor mortis, this organ being affected at a time (in animals, after three to five hours) in which rigor mortis cannot be demonstrated in any of the skeletal muscles.

III. Necrosis.

§ 48. The condition of *local death*, or death of individual cells or groups of cells, is known as **necrosis**. As the result of necrosis the functions of the affected tissue are forever lost.

The necrosis of a cell-group or of an entire organ is only under certain conditions immediately associated with recognizable changes of structure. The slight histological changes which the cells undergo during their death do not always permit us to determine with certainty the exact moment of cessation of life; nor does the macroscopic appearance of the visible portions of the body always inform us when a portion thereof becomes necrotic.

Necrosis is therefore evident upon anatomical investigation only when certain changes in structure have occurred, either coincidently with the death or subsequently thereto. Necrosis is shown immediately by histological changes only in the case of the action of a limited number of injurious agencies; in all other cases the necrosis is followed by such changes after a longer or shorter interval. According to the nature of the subsequent tissue-changes it is possible to distinguish different varieties of necrosis.

Histologically the **necrosis of a cell** is shown in the first place by the *disintegration and disappearance of the nucleus*, whereby the chromatin of the cell—that part taking nuclear stains—forms small clumps and granules which at times pass out from the nucleus into the cell-protoplasm,

where they become dissolved and disappear (*karyorrhexis*). At other times the nucleus before its disappearance shows *signs of shrinking*, and in this condition takes the nuclear stain more deeply than under normal conditions (*pyknosis*). In other cases the nucleus *retains its form but loses its staining power with nuclear stains*, and then dissolves and disappears (Fig. 35, *c*, *d*), so that in well-fixed and stained preparations no trace whatever of the nucleus can be found (*karyolysis*). Thus, for example, in an anæmic infarct of the spleen or kidney caused by arterial embolism the nuclei of the spleen and kidney cells are lost very soon after the death of the tissue (Fig. 36, *c*, *d*, *f*, *g*). At the same time the affected area becomes strikingly pale, cloudy, yellowish-white, or cream-colored; so that the occurrence of the necrosis may be recognized by the naked eye.

The *protoplasm* of the dying cells sooner or later also undergoes *changes*, which, according to the mode of death, may in some cases begin before the cells die, or in others may take place only after the cells are dead. The kind of change is dependent upon three factors: the nature of the cells themselves, the character of the destructive influence, and the amount and character of the fluids surrounding and infiltrating the cells. Amœboid cells usually assume a *globular form* after death. Delicate and only slightly modified cell-bodies, rich in protoplasm, often become, before or after death, markedly *granular*, less frequently *homogeneous* and *lumpy* (Fig. 35, *c*, and Fig. 36, *e*). Through the taking-up of fluid the protoplasm or even the nucleus may become *swollen* and show *drops of fluid* (*vacuoles*); and this may lead to breaks in the continuity of the protoplasm (*plasmoschisis*). Not infrequently as a result of plasmoschisis *portions of the cell may be extruded* or *cut off by constriction*. The ultimate end of all these changes is the *disintegration of the protoplasm and the nucleus into granular masses*, this process being often accompanied by a formation of fat.

FIG. 35.—Necrosis of the epithelium of the urinary tubules in icterus gravis. (Müller's fluid, gentian violet.) *a*, Normal convoluted tubule; *b*, ascending portion of the loop; *c*, convoluted tubule with necrotic epithelium; *d*, convoluted tubule with only a part of its epithelium necrotic; *e*, normal stroma with blood-vessels. × 300.

Cells which normally undergo a marked transformation, as is the case with cells showing cornification, usually present less striking changes; yet even these may swell and finally become dissolved. The morphological changes in dead cells are the least pronounced when the dying cells become *more condensed and dry* (*inspissation*). In this case the cells only become smaller, yet it is often seen that after the loss of the nucleus the cells become changed into *lumpy masses*.

The injurious influences which may give rise to necrosis may be divided into five groups. The first two include those which destroy the tissue directly—**mechanical and chemical forces.** A third group of **injurious influences comprises those of a thermal character.** The elevation of the temperature of a tissue to 54°–68° C. for any length of

time leads to its death. Higher temperatures act more quickly. Refrigeration to low temperatures likewise can be borne but a short time. A fourth group is caused by **infection** with animal or vegetable parasites. A fifth group is caused by **a cessation of the supply of nourishment and oxygen to the tissues**, and is known as **anæmic necrosis** or **local asphyxia** (*Fig. 36*).

Fig. 36. From the edge of an anæmic infarct of the kidney. (Müller's fluid, hæmatoxylin, and eosin.) *a*, Normal kidney tissue; *a*₁, normal kidney-tubules with stroma infiltrated with leucocytes; *b*, normal glomerulus; *c*, necrotic tissue without nuclei, showing granular coagula in the tubules; *d*, necrotic swollen glomerulus with few nuclei; *e*, tubules without nuclei in a stroma still containing nuclei; *f*, necrotic tissue with nuclei; *g*, with hæmorrhagic infiltration. × 50.

All those factors which *seriously affect the circulation within any part* and lead to a *stoppage of the blood-supply*—such as thrombosis, embolism, closure of a vessel as a result of continued abnormal contraction, disease of the vessel walls, or ligation, pressure on the tissue, inflammation, hæmorrhage, etc., may lead to necrosis of tissue. Not only a permanent cessation of the circulation, but also a temporary stoppage of the same lasting beyond a certain time, leads to the death of the affected tissue. Whether or not hæmorrhage occurs in such cases is immaterial, as was stated in § 44, and influences only the appearance of the affected part. *Hæmorrhagic infarction* has, therefore, precisely the same significance as an *anæmic necrosis associated with hæmorrhage*.

When death follows quickly upon the action of an injurious agent, it is spoken of as **direct necrosis**. When it occurs slowly and is preceded by different tissue degenerations it is designated **indirect necrosis** or **necrobiosis**.

Mechanical, chemical, thermal, and infectious sources of injury, as well as anæmia, may act coincidently, or separately, one after the other. When the tissue is damaged by any one of the first-named group of injurious influences, the blood itself very often suffers a change which leads to stasis and coagulation in the capillaries, as well

as in the veins and arteries, and in this way the circulation may be arrested.

Whether or not a given injury will cause necrosis of the tissue depends, not only upon its nature and severity, but also chiefly upon the condition of the tissue at the time of the injury. A tissue whose vitality has already been lowered as the result of long-continued disturbances of circulation, general marasmus, hydræmia, changes in the composition of the blood, etc., dies more easily than when in a normal condition. In severe cases of typhoid fever relatively slight pressure on the trochanters, elbows, sacrum or heels, etc., may suffice to bring about a gangrenous necrosis of the skin and subcutaneous tissues. Such forms of necrosis are known as **marasmic necrosis** or **marasmic gangrene,** and as **decubitus** or **decubital necrosis.**

The **course of necrosis**—that is, the tissue-changes resulting from the death of cells—is dependent upon the character of the affected tissue, its location, the manner of its death, and the cause of the necrosis. Further, the amount of lymph and blood in the tissue, and the opportunity afforded for the access of air and putrefactive organisms, also exert a very important influence. Tissue-changes which preceded the necrosis, such as fatty degeneration, inflammation, hæmorrhage, etc., are also of significance in determining the character of the necrosis.

As the **result of the necrosis of a certain tissue-area,** there always develops an *inflammation of greater or less intensity in the surrounding tissues* (Fig. 36, *f*). This reactive inflammation is most marked when the necrotic area becomes gangrenous. Through the formation of an inflammatory zone the necrotic area becomes marked off from the surrounding tissue, and is isolated or sequestrated; this process is spoken of as a *sequestrating or limiting inflammation,* and the dead area thus shut off is called a *sequestrum.* A more detailed description of these inflammatory processes will be found in Chapter VII.

Five chief **sequelæ** of necrosis may be distinguished: 1. The dead tissue may be removed by *absorption,* or may be *cast off* from the surface, and *its place taken by normal tissue* (*regeneration*). 2. The dead tissue is similarly removed, but instead of the normal tissue being restored, the defect is filled wholly or in part by the formation of connective tissue, the so-called cicatricial tissue. 3. The necrotic tissue is cast off or liquefied, the defect is not filled in. and there remains an *ulcer.* Should this heal without regeneration of the lost tissue there remains a *defect.* 4. The necrotic tissue is partly absorbed, but a portion remains as a *sequestrated necrotic mass* which not infrequently later becomes *calcified* and *surrounded by a connective-tissue capsule.* 5. The fifth sequela of necrosis is *cyst-formation.* The necrotic area becomes encapsulated by connective tissue, the dead tissue becomes absorbed and is replaced wholly or in part, usually at the periphery, by new tissue, or it may be liquefied, and the space filled with fluid, forming a *cyst.* This sequela of necrosis occurs most frequently in the brain.

By many writers there is recognized besides these forms of necrosis an especial group designated as **neuropathic necrosis,** that is, a necrosis resulting from a lesion of the central or peripheral nervous system. By some the esssential cause of such necrosis is referred to a lesion of the trophic nerves, while others refer it to disturbances of circulation, continued pressure, and mechanical injury of anæsthetic and paralyzed portions of the body. According to observations thus far made upon men, as well as

upon experiments in animals, external injuries and disturbances of the circulation play the most important rôle in the production of this form of necrosis, and can never be wholly excluded.

The time required to kill tissue by the shutting-off of the circulation varies with the different tissues. Ganglion-cells, kidney epithelium, and liver-cells die in two hours, while surface epithelium and connective tissue may live for twelve hours or longer. Epidermis under certain conditions may remain alive for a number of days, and still retain its power of proliferation (see Transplantation).

Karyorrhexis, karyolysis, and tissue liquefaction occur also in putrefaction. Tissue preserved under aseptic precautions, and protected from bacteria in moist chambers at the body temperature, also loses its nuclei. Liver-tissue shows this change most rapidly and completely, the tissues of the spleen and kidney more slowly and less completely, so that all nuclei may not have disappeared after eight to fourteen days. The disappearance of the nucleus occurs only in the presence of a relatively abundant supply of fluid, and may be prevented by desiccation of the tissue.

§ 40. According to the various conditions in which the tissues may be found after they have died, **four chief forms of necrosis** may be distinguished: *coagulation-necrosis, caseation, liquefaction-necrosis*, and *gangrene*.

Coagulation-necrosis (Weigert, Cohnheim) is characterized by the occurrence of coagulation, either *extracellular*, in the fluids about the cells; or *intracellular*, in the latter case leading to peculiar changes within the cells.

Fig. 36. Coagulation-necrosis in the interior of a greatly swollen mesenteric lymph-gland, from a case of typhoid fever. (Alcohol, fibrin stain.) Network of fibrin between the necrotic cells. × 400.

As *coagulation-necrosis with extracellular coagulation* may in the first place be regarded both the intravascular (Figs. 14–17) and the extravascular *coagulation of the blood*, inasmuch as this phenomenon may be regarded as the death of the blood; and in fact a destruction of cells does occur. Further, there may be considered as belonging to this class the various forms of coagulation which occur in inflammations, partly on the surface and partly in the interior of the tissues (see Chapter VII.); and which are characterized by the formation, in some cases of stringy fibrin (Fig. 37), in other cases by the formation of granular or hyaline masses of coagula.

Intracellular coagulation occurs when dead cells or cell-products are infiltrated with a fibrinogen-containing lymph. The cells lose their nuclei, present either a granular (Fig. 33, c, d, and Fig. 36, c, d, e) or a hyaline lumpy appearance. They remain in this condition for a certain time and then break down into granules and become dissolved.

This phenomenon is most frequently observed in anæmic, toxic, and thermal tissue-necroses, as for example, in anæmic infarcts of the kidney (Fig. 40) and of the spleen, also in many inflammations which are associated with marked infiltration of the tissues (Fig. 37), due to exudation from the blood-vessels. In the necrosis of striped muscle, which is of very frequent occurrence in typhoid fever, the contractile substance acquires a hyaline waxy appearance and breaks up into hyaline lumps (Fig. 38, b).

The necrotic tissue of anæmic infarcts looks pale yellowish-white, or yellow-coloured. Muscles containing many dead fibres in a state of hyaline coagulation are pale red, and of a dull lustre, resembling fish-flesh.

Inflamed tissues undergoing coagulation necrosis are likewise cloudy, opaque, and grayish-white; but the color may undergo marked changes through the admixture of blood or the imbibition of bile, as in the intestine, for example.

The structure of a tissue which is the seat of a coagulation-necrosis, may still be clearly recognized if only the more delicate parts have been destroyed. When all parts have been changed, the entire tissue may be converted into a structureless, hyaline, or granular mass, containing no nuclei or but few. This change takes place very often in the necrosis of inflamed tissues which are infiltrated with exudate. Through the proper treatment of preparations there may be frequently demonstrated in these necrotic areas an intercellular stringy fibrin; this is seen occasionally in anæmic infarcts, but more often in inflammatory tissue-necroses (Fig. 37).

FIG. 38.—Hyaline necrosis or waxy degeneration of muscle, from a case of typhoid fever. *a*, Normal muscle-fibre; *b*, degenerated fibres, which have broken up into hyaline lumps; *c*, cells lying within the sarcolemma; *d*, connective tissue infiltrated with cells. × 250.

Caseation is a form of necrosis closely related to coagulation-necrosis, and is characterized by either a hard or a soft cheesy appearance of the necrotic area. In the first case the dead tissue is like firm, yellowish-white, hard cheese, or similar to raw potato; in the second case it is white, soft, sometimes dry, sometimes moist, and not infrequently resembling thick cream.

Typical caseation occurs most frequently in *tubercles* and represents the characteristic end of the retrogressive changes in this condition. It also occurs in syphilitic granulomata and in very cellular tumors; inflammatory exudates may also become changed into cheesy masses.

The process of caseation of cellular tissues, which is a characteristic of tuberculous granulations, takes place gradually, and is therefore to be regarded as a form of **necrobiosis**. The cells are changed successively into non-nucleated, homogeneous, lumpy masses, which later disintegrate and break up into a granular mass (Fig. 39, a_1, a). At the same time with these changes there often appears between the cells a hyaline substance, sometimes forming a framework around the cells or at other times more lumpy or granular, and fibrin-like—the so-called "*fibrinoid substance.*" *Typical fibrillated fibrin* (Fig. 40, *a*) staining deep blue with Weigert's fibrin stain is often also present. It may therefore be assumed that both substances represent coagulation-products of a fluid which has escaped from the blood-vessels.

FIG. 39.—Tissue from a partly caseated tuberculous focus, containing bacilli. (Alcohol, fuchsin, aniline blue.) *a*, Granular; a_1, lumpy masses of cheesy material; *b*, fibrocellular tissue; *c*, partly necrotic giant-cell containing tubercle bacilli; *d*, bacilli in the cellular tissue; *e*, bacilli in necrotic tissue; *f*, bacilli enclosed within cells. × 200.

Through progressive cleavage and disintegration of the dead cells, the fibrinoid substance, and the fibrin, the dead tissue is ultimately

changed into a finely granular mass, in which no traces of the original structure can be perceived.

The cheesy metamorphosis of the fibrino-cellular exudate, which is found especially in the alveoli of the lungs in the neighborhood of tubercles, is brought about similarly by the disappearance of the nuclei, and the disintegration of the cells and fibrin into a non-nucleated granular mass.

The granules of the soft cheesy masses in tuberculous and non-tuberculous foci are chiefly albumin granules, more rarely fat-droplets. The ultimate fate of such masses may be partly *liquefaction* and *pultaceous softening*, partly *absorption*, and partly *desiccation* and *calcification*.

Colliquation or **liquefaction-necrosis** is characterized especially by the fact that the *necrotic parts become dissolved in the fluids present in the*

FIG. 40.—Fibrin-containing tubercle from the lung. (Alcohol, hæmatoxylin, fibrin stain.) *a*, Fibrin; *b*, giant-cell; *c*, cellular portion of the tubercle. × 300.

tissues. The dissolution may be accomplished by swelling and liquefaction, as well as by a breaking up of the tissue-elements, or through a combination of these processes. Thus, for example, in burns of the second degree the cells of the epidermis, which have been killed by the heat, with the exception of the horny layer, become dissolved in the fluid exuding from the papillæ (Fig. 41, *d*, *f*). In the case of anæmic infarcts of the brain the *necrotic* brain-substance undergoes softening with the formation of drops and granules, and becomes converted into a milky, pultaceous mass in which the products of the destruction of the brain-tissue disintegrate into smaller and smaller particles, which, either free or enclosed within cells, become absorbed or completely dissolved. In suppurative processes of the tissues, which occur very frequently in purulent inflammations, the necrotic tissue is dissolved in the fluid vascular exudate containing pus corpuscles.

Necrosed areas in the mucosa of the stomach become dissolved through the digestive action of the gastric juices.

Coagulation and *liquefaction* may not infrequently follow or precede

each other. For example, the products of coagulation in an inflamed area may again become dissolved. In gangrenous blebs produced by the dissolution of epithelial cells, there may occur a coagulation, the products of which are later again dissolved. Necrotic foci arising in the course of inflammations or in granulomata very often at a later stage become liquefied.

In the case of both the *coagulation* and the *liquefaction* of tissues the process depends essentially upon the **action of ferments**, which are combined in part with living protoplasm and in part are contained in the dead tissue. The liquefaction of tissue by tissue-ferments is designated **autolysis.** The action of the **autolytic ferments** takes place also in portions of tissue that have been kept aseptic outside of the body, or preserved in antiseptic fluids (chloroform water) that inhibit the growth of bacteria. There occurs a liquefaction of the tissue with the formation of various products of decomposition.

The changes described above as occurring in dead or dying tissues are not the only ones which take place during tissue-destruction. They are only the chief types which occur in the course of a relatively rapid necrosis. Many of the tissue-degenerations described in the following paragraphs also lead, not infrequently, to ultimate death of the tissue, and consequently they must be regarded as belonging to the processes classed as *tissue-necrobiosis*. Granular degeneration, fatty degeneration, mucous degen-

FIG. 41.—Blister of cat's paw, caused by hot sealing-wax. (Alcohol, carmine.) *a*, Horny layer of the epidermis; *b*, rete Malpighii; *c*, normal papilla; *d*, swollen epithelial cells whose nuclei are in part visible, and in part have disappeared; *e*, epithelial cells lying between the papillæ, the upper ones swollen and elongated, the lower ones preserved; *f*, total liquefaction of the epithelium; *g*, swollen cells of the interpapillary cell-masses, which have lost their nuclei; *h*, a similar cell-mass which has been completely destroyed, and raised from the basement-membrane, by the coagulated subepithelial exudate *k*; *i*, flattened papillary body infiltrated with cells. × 150.

eration, and hydropic degeneration often end in the destruction of cells; and the same result may be reached in the case of hyaline and amyloid degeneration of the connective-tissue, in that not only the ground-substance of the tissue is permanently altered, but the cells of the affected tissue also die.

According to the investigations of *Schmaus* and *Albrecht*, kidney epithelium soon becomes invisible in water, salt solutions, and diluted alkalies, in that the cells become swollen or dissolve. Epithelial cells which have become granular through anæmic necrosis retain their granular structure in the solutions named. This may be taken as a proof that coagulation has occurred with the formation of firm bodies, not soluble in dilute acids, alkalies, and neutral salts, out of elements occurring originally in the cells in a fluid state.

The number of **enzymes** contained in the tissue-cells is very great. *Hofmeister* ascribes to the liver-cells at least ten. In these cells there surely occur a proteolytic

enzyme (tryptase) which disintegrates the albumin-molecule, a ferment-splitting nucleo-proteoid and nucleinic acid, and a diastatic ferment changing glycogen into sugar. Proteolytic enzymes occur probably in the most varied tissues, perhaps in all (*Salkowski*, l. c.). At the present time we do not know whether they are active under physiological conditions, or whether they are present in the cells only as inactive proferments or zymogen, which first become active during or after the death of the cells under the influence of a "kinase." In order to decide these questions it would be necessary (*Salkowski*) to show accurately the characteristics of the products of autolysis of different organs and to seek out the specific autolytic products also in the corresponding organs of freshly killed animals. A splitting of nuclein-substances by ferments during life is shown positively by the fact (*Salkowski*) that purin bases, the specific products of nuclear disintegration, can be demonstrated in all fresh organs.

§ 50. Under the name of **gangrene** may be classed those forms of necrosis in which the tissue, partly through exposure to the air, partly through the agency of bacteria, suffers changes which are similar in appearance to those occurring in burned tissues. If necrotic tissue through exposure to the air loses its water by evaporation and becomes dry, the condition is designated **dry gangrene** (*gangræna sicca*) or **mummification**. When the dead part remains moist, the terms **moist gangrene** (*gangræna humida*) or **sphacelus** may be applied. If through the agency of bacteria there occurs a *foul-smelling putrefaction*, the condition is known as a **putrid gangrene** (*gangræna fœtida*). Development of gas-bubbles as a result of the putrefactive changes leads to **emphysematous gangrene** (*gangræna emphysematosa*).

Moist gangrene and putrid gangrene are in general identical, since bacteria can develop only in moist tissues. Nevertheless a dry gangrene is not infrequently a putrid gangrene, since bacteria may develop in the tissue before drying takes place. Dry gangrene may also develop from a moist gangrene, or through the absorption of water become changed into the latter.

When the dead tissue, in either mummification or moist gangrene, contains a large amount of blood, it appears black, dark brown, or greenish-black in color, and is then called **black gangrene.** If, on the other hand, the dead tissues are anæmic, the condition is sometimes spoken of as **white gangrene,** although there is more or less discoloration of the dead part, so that the expression is often inappropriate.

In the case of gangrene of superficial parts of the body, there may be distinguished, according to the temperature of the dead part, a *cold* and

FIG. 42.—Dry gangrene of the toes, due to calcification, narrowing, and obliteration of their arteries.

a *warm* or *hot gangrene*, the latter designation being used when the gangrenous area is kept warm by the blood flowing through the neighboring tissues.

Gangrene may be caused by external injuries, heat, cold, corrosives, crushing, pressure, infection, etc., as well as by disturbances of the circulation.

Gangrene due to disturbance or arrest of the circulation occurs not infrequently in old people (*senile gangrene*), involving the extremities, particularly the toes, feet, and legs. It is usually of the dry variety, and is dependent partly upon general disturbances of the circulation and partly upon disease of the artéries of the extremities (calcification, ossification, thickening of the intima, thrombosis, embolism) (Fig. 42). The dying parts appear bluish-black as a result of the venous stasis.

Gangrene from cold affects chiefly the tips of the extremities, nose, and ears, and is characterized by changes similar to those described above.

Gangrene from heat is confined to the area directly affected by the heat.

Pressure-gangrene or **decubitus** (*bedsore*) occurs in marasmic individuals, most frequently upon the sacrum and the heels, both of which regions are exposed to pressure when the individual lies upon his back. The bedsore begins with the formation of bluish-red spots, within whose area the tissue dies, and through the agency of bacteria undergoes decomposition and finally disintegrates. The gangrenous area may be of large extent, especially when over the sacrum; the bone may be laid bare over a large area through the destruction of the overlying soft parts.

Toxic gangrene occurs chiefly in ergot poisoning as a result of the contraction of the small vessels and formation of thrombi. The tips of the extremities are usually affected.

Infectious gangrene occurs particularly in different infections of the skin and subcutaneous tissue, and may be associated with gas-formation. In the form known as *foudroyant gangrene* different varieties of bacteria have been found; the bacillus of malignant œdema, an anaërobic bacillus (Welch, E. Fränkel, Hitschmann and Lindenthal), proteus (Hauser), and bacterium coli. Infections associated with putrid gangrene may occur in the internal organs, but affect chiefly the lungs and intestines.

A so-called **neuropathic gangrene** occurs when a tissue affected with either sensory or motor paralysis is wounded or subjected to continued pressure. It is dependent partly upon circulatory disturbances and partly upon infection. Gangrene resulting from the withdrawal of the influence of trophic nerves has not yet been demonstrated. **Symmetrical gangrene,** which affects corresponding parts of the extremities and has been regarded by many as a neuropathic disease, is dependent upon changes in the blood-vessels; likewise, the perforating ulcer of the foot (*mal perforant du pied*), which begins as a callosity following mechanical influences, and is characterized by an accompanying gangrene which rapidly penetrates into the deeper tissues, is dependent upon the closure of an artery of the foot.

In moist gangrene the tissues break down with a varying degree of rapidity, the fasciæ resisting for the longest time. As crystalline products of the chemical changes there may be found needles of fat and tyrosin, spherules of leucin, coffin-lid crystals of triple phosphate, and crystals of hæmatoidin. If the gangrene comes to a standstill, the gangrenous tissue becomes sequestrated through the formation of a zone of demarcation—that is, becomes separated from the living tissue, and under favorable conditions may be thrown off from the body. In the case of necrotic portions of bone a very long time is required for sequestration. Extension of gangrene (through infection or continued circulatory disturbance) leads sooner or later to death, especially if toxic substances or bacteria are taken up into the blood or lymph.

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IV. Hypoplasia, Agenesia, and Atrophy.

§ 51. **Hypoplasia**, or the defective development of anlage, may affect

either the body as a whole or only single organs or parts of organs, and may occur either during the period of intra-uterine development or later during the period of post-embryonal development.

When either the entire skeleton or at least the greater part of it is under-developed, and especially if the bones do not attain their normal length, the affected individual is abnormally low in stature, and is called a *dwarf* (Figs. 43 and 44). The individual parts may be fairly well proportioned (Fig. 43), or they may be unsymmetrically developed (Fig.

FIG. 43. FIG. 44.

FIG. 43.—Skeleton of a female cretin, thirty-one years of age, 118 cm. in height, with klinocephalic skull. The cartilage sutures of the diaphyses of the long bones and pelvic bones still show; as does also the frontal suture. The individual parts of the skeleton are, on the whole, in the proper proportion, the upper extremities alone being relatively short.

FIG. 44.—Skeleton of a female dwarf of fifty-eight years of age, 117 cm. in height, with very short extremities, and long trunk. The cartilage sutures are still present; the articular ends of the bones are thick.

44). For example, the trunk may be of normal size, while the extremities are abnormally short (Fig. 44); or both the trunk and the extremities may be abnormally small, while the head is of normal size, and consequently appears relatively too large for the small body. When the lack of development affects individual parts of the skeleton exclusively, or if it is more marked in certain parts than elsewhere, there results a

stunting of individual portions of the body. For example, defective development of the cranium gives rise to *microcephalus* (Fig. 45) and *micrencephalus* (Fig. 46); through defective development of the humerus or of the bones of the hand there results a shortening of the upper arm or of the hand; and through hypoplasia of the lateral masses of the sacrum the transverse diameter of the pelvis becomes diminished.

Of the individual organs the central nervous system (Figs. 46

FIG. 45.—Head of Helene Becker (microcephalic), at age of five years. (From a photograph taken by A. Ecker, in 1868.)

FIG. 46.—Brain of Helene Becker (microcephalic) who died at the age of eight years. (After von Bischoff.) This brain weighed 219 gm. (instead of 1,377 gm., according to Vierordt).

and 47), and the genito-urinary tract in particular suffer very frequently a stunting of development, although the intestines, heart, lungs, liver,

FIG. 47.—Hypoplasia and microgyria of the left cerebral hemisphere, from a deaf-mute. *a*, Right hemisphere; *b*, left hemisphere; *c*, occipital lobe presenting a condition of microgyria; *d*, membranous cyst in the region of the parietal lobe. (Seen from above, after removal of the cerebellum. Two-thirds natural size.)

etc., do not escape similar disturbances of growth. For example, the entire brain (Fig. 46), or only one of the hemispheres, or a part of the latter (Fig. 47, *c*, *d*) may fail of complete development. The intestine

FIG. 48.—Hypoplasia of the uterus with well-developed ovaries, but without ripe follicles. From a cretin, twenty-eight years of age.

may in part be represented by a thin canal incapable of functionating (Fig. 49, *d*), or even by a solid cord (Fig. 49, *e*). The uterus not infrequently remains in an undeveloped state (infantile) (Fig. 48), and occasionally at the time of puberty the ovary (Fig. 50, *e*), or the entire internal generative apparatus, and at times also the external organs may remain in the undeveloped state of the young child. A more or less marked hypoplasia of the kidney is not rare. In the development of the respiratory tract the alveoli of a portion of the lung may wholly fail to develop.

The above-mentioned examples of hypoplasia, to which many others might be added, arise partly through intrinsic causes inherent in the germ, and are therefore inheritable, and partly through the action of extrinsic injurious influences upon normal anlage during the course of development. For example, the growth of the bones may be influenced and retarded by imperfect function of the thyroid gland or disuse, and inflammation. Total failure of portions of the body or of single organs to develop is known as **agenesia.** This condition is dependent either upon the non-formation of the anlage, or upon the destruction of the latter after they have begun to develop. (See chapter on Malformations.)

FIG. 49.—Hypoplasia of the small intestine of the new-born child. *a*. Greatly dilated portion; *b*, *c*, *d*, *e*, portion showing great narrowing and stunting; *f*, normally developed portion. (Five-sevenths natural size.)

The tissue composing hypoplastic organs or parts of organs, though of less bulk than normal, may present no abnormalities of structure. In other cases there may be associated with the smallness of size a disturbance of internal **organization**, so that often the more highly specialized elements of the organ fail of development, the ***hypoplasia being at the same time associated with an agenesia of individual parts.*** Thus, for example, in hypoplasia of the ovary (Fig. 50, *e*) the development of the ova and the ripening of the follicles may fail in part; in hypoplasia of the brain there may occur at the same time a defective development of the gan-

Fig. 50.—Cross sections of ovaries at different periods of life. (Hæmatoxylin and eosin.) *a, b, c, d,* Normal ovaries; *a*, girl of five years; *b*, twenty-three years; *c*, twenty-nine years; and *d*, twenty-one years; *e*, hypoplastic ovary of girl of twenty-seven years; *f, g*, senile ovaries from women of eighty and eighty-three years of age. (Natural size.)

glion-cells and nerve-fibres, and at times portions of the brain may consist only of membranous masses (Fig. 47, *d*) in which no ganglion-cells are present. In hypoplasia of the lung there may be under certain conditions a complete failure of development of the alveoli, so that the lung-tissue consists merely of a very vascular connective tissue throughout which lie the bronchi, the latter in the course of time usually becoming dilated.

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See also Chapter IX.

§ 52. **Atrophy** is a diminution in the size of an organ due either to a diminution in size or disappearance of its individual elements. It may occur at any period of life, and is a very common result of many pathological processes. Within certain limits it may be regarded as a ***physiological phenomenon***, in that in old age there constantly occurs a certain degree of retrograde change in all the organs, associated with a diminution in their size. Certain organs undergo such an atrophy with partial or total loss of their functional power, even before old age, as, for example, the thymus, which atrophies completely even before the end of the period of growth; and the ovary (Fig. 50, *f, g*), a part of whose ova are discharged during the period of sexual activity, the remainder being

destroyed. In old age the lymphadenoid tissues, the muscles and bones, in particular, suffer atrophy, though the tissue-changes of senility vary greatly in different individuals, so that often other tissues, the glandular organs or the brain, show the most marked atrophy.

The atrophy of an organ is characterized chiefly by its diminution in size. In atrophic conditions of the muscles (Fig. 51) the affected portions of the body become smaller, and in extreme cases the extremities appear as if consisting only of skin and bones. When the atrophy of an organ is uniform throughout, its normal shape may be preserved; but if the atrophy progresses more rapidly in certain parts than in others, the surface of the organ may show local depressions (Fig. 53) and cicatricial contractions (Fig. 56), so that the organ, for example, the liver or kidney, may present a knobbed or granular appearance. When tissues which are undergoing atrophy are prevented from contracting, as in the case of the bones and lungs, the external form is preserved. In the case of bone, the medullary spaces and the Haversian canals become enlarged, and a condition results which is known as *excentric atrophy* or *osteoporosis* (Fig. 52). In the lungs the alveoli become confluent into large air-spaces as the result of the disappearance of the intervening walls.

In atrophy of the glands and muscles there occurs frequently a change of color, though this is of secondary importance. Either the *normal pigmentation* of the affected organ is brought out *more distinctly* by its atrophy, or associated with the atrophy there is a *deposit of pigment* (*brown* or *pigment atrophy*), or finally the change of color may be dependent upon the changed blood-content of the atrophic tissue.

The diminution in size of atrophic organs is the result of a diminution in size and disappearance of the histological elements composing them. In the majority of the organs, particularly in the glands, muscles, and bones, the specific cells which perform the especial function of the affected organ, are affected in atrophy to a far greater degree than the supporting connective-tissue framework. Indeed, it may be frequently observed that the connective-tissue elements may be wholly preserved, or even increased in number, while the more highly specialized elements have disappeared. Thus, for example, in atrophic muscle (Fig. 54) the contractile substance within the sarcolemma (a) may disappear to a very great extent (b) without the occurrence of any atrophy whatever of the connective tissue between the muscle-bundles. The nuclei (c_1) of the connective tissue may even be increased in number.

FIG. 51.—Juvenile muscular atrophy. (Case observed by de Souza.)

In atrophy of the kidney the epithelial cells of the urinary tubules (Fig. 55, *a*) become smaller (*f*) and may finally wholly vanish so that the tubules collapse. Likewise, the epithelium of the glomeruli (*d*) is lost, while the capillaries become obliterated.

The same thing occurs in simple atrophy of the liver, in that all the liver cells of a lobule may disappear without any perceptible decrease of the supporting reticulum. Likewise the ganglion cells of the brain and spinal cord may atrophy without the neuroglia being diminished. Not infrequently the latter may become increased.

In atrophy of the bones the true bone-tissue becomes diminished. In atrophy of the bone-marrow the total mass of free marrow-cells is diminished. The supporting cells may in consequence take up an increased amount of fat; but, on the other hand, the fat in the cells of the marrow may also vanish, so that free spaces which become filled with fluid are formed between the supporting cells.

In atrophy of the lymph-glands and of the spleen the free cells in particular disappear and in parts are completely absent.

The changes leading to atrophy may take place without the occurrence of any apparent change of structure in the individual tissue-elements (Fig. 54), so that the condition of atrophy is reached essentially through a loss of volume of the individual parts. Both the cell-body and the nucleus may become smaller; and the latter change may be observed particularly in the liver in cases of starvation-atrophy (Lukjanow). This form of atrophy is known as **simple atrophy**, and is to be distinguished from the **degenerative atrophies**, in which the *tissue-elements during the progress of the atrophy show changes in their structure*, and frequently contain pathological substances. Thus a cell may become granular, and undergo fragmentation, or may swell up and liquefy, or there may be formed within the cell drops of fat or mucus; all of these changes signifying degenerative conditions of the cell-protoplasm. These processes are classed as special *forms of degeneration* and will be discussed in the paragraphs of the following section. Degenerative changes can occur at the same time in the nuclei, as shown by fragmentation, distorted shape, clumping of the chromatin, diffusion of chro-

FIG. 53.—Excentric atrophy of the lower end of the tibia and fibula, with osteoporosis. (Natural size.)

matin into the cell-protoplasm, swelling and liquefaction of the nucleus. All these processes lead ultimately to the disappearance of the nucleus and the destruction of the cell.

The degenerations leading ultimately to a condition of atrophy of the affected organ are of very frequent occurrence, particularly in glandular

FIG. 53.—Senile atrophy of the skull-cap, with defect of the external table and the spongy portion throughout the central portion of both parietal bones.

organs. The process is often complicated by the occurrence of inflammation.

According to their genesis the **forms of atrophy** may be classed as **active** or **passive.** In the former the cell is no longer able to make use of the food brought to it; in the latter the food is either not supplied to the cell in sufficient quantity or in the proper form, or harmful substances are brought to the cells which impair their function. Active

FIG. 54.—Section of an atrophic muscle, from a case of progressive muscular atrophy. (Müller's fluid, Bismarck brown.) *a*, Normal muscle-fibres; *b*, atrophic muscle-fibres; *c*, perimysium internum, the nuclei of which, at c_1, seem to be increased in number. × 200.

atrophy is particularly a part of *senile degeneration* (see above), but it occurs also under pathological conditions, especially in the case of nerves, glands, and muscles (Fig. 51) whose functional activity is not called into play.

The clinician ordinarily prefers another classification of atrophy;

namely, senile atrophy, atrophy due to impaired nutrition, pressure atrophy, atrophy of disuse, and neuropathic atrophy.

Senile atrophy (Fig. 53) is partly active, and partly passive, in that it is not simply the result of the diminishing vital energy of the cell, but also depends in part upon the narrowing and obliteration of the vessels conveying nourishment to the cells. It may occur in all the organs, but is often more marked in one organ than in another. The bones, kidneys, liver, brain, and heart may undergo a marked loss of volume.

FIG. 55.—Senile atrophy of the kidney. (Alcohol, alum-carmine.) *a*, Normal urinary tubules; *b*, normal glomerulus; *c*, stroma with blood-vessels; *d*, atrophic and obliterated glomerulus; *e*, small artery, with thickened intima; *f*, atrophic and collapsed urinary tubules. × 200.

Atrophy due to impaired nutrition may result in the first place from an insufficient supply of food to the body as a whole, or from extensive loss of the fluids of the body. In these cases the whole body is affected, though the fat, blood, muscles, and the abdominal organs suffer to a greater extent than the remaining tissues. Local atrophies may result from local disturbances of circulation, and are the frequent sequelæ of *diseases of the arteries* in which the vessel lumen is narrowed (Fig. 56). Further, they are of frequent occurrence as a result or a part of inflammatory processes; but it should be noted that in these cases the condition is not of the nature of a simple atrophy, but rather of various *degenerative changes* leading to the death of the cells and of the tissues.

At times atrophy results from the presence of deleterious substances in the blood. For example, iodine causes a diminution in the size of the thyroid gland. In chronic lead-poisoning the extensor muscles of the forearm in particular become atrophic.

FIG. 56.—Arteriosclerotic atrophy of the kidney. (Natural size.)

Pressure-atrophy occurs when a tissue is subjected for a length of time to a moderate pressure (Fig. 57). It depends partly upon direct injury to the tissues and partly upon disturbance of the circulation. The most typical examples are: the atrophy of the liver caused by the

pressure of the edge of the ribs upon the organ due to tight-lacing ("corset-liver"), and the disappearance of bone (Fig. 57) following the pressure of an aortic aneurism, tumors, or of an accumulation of fluid in the ventricles of the brain.

Atrophy of disuse occurs in the muscles, glands, bones, skin, and other tissues, and is dependent upon the disuse of the organ in question. In the case of muscles and glands the atrophy is essentially active; the nutritive processes diminishing as the result of the lessened functional activity. In the other tissues the atrophy is essentially dependent upon the lowering of nutrition of the disused parts, though a change in the power of assimilation of the cells cannot be wholly excluded. When the inactivity occurs during the period of development, and the tissue as a result becomes stunted, the condition is to be regarded as a hypoplasia, though no sharp line can be drawn between hypoplasia and atrophy, since in the former there may be also a disappearance of structures which had undergone a certain degree of development.

FIG. 57.—Pressure-atrophy of the spinal column, due to pressure by aortic aneurism.

Neuropathic atrophy is a result of diseased conditions of the nervous system, and is apparent most often in an atrophy of the nerves and muscles, though other tissues may be affected. For example, after destruction of the anterior horns or of the motor roots of the spinal cord, there follows an atrophy of the corresponding nerves and muscles. After injury of the peripheral nerves the skin often becomes atrophic. According to many authors, disease of the nerve-trunks of one side of the face is followed by a *unilateral neuropathic facial atrophy* (Fig. 58), but by others (Möbius) the neuropathic nature of this condition is contested. Unilateral affections of the brain in fœtal life or during childhood may lead to atrophy of the opposite side of the body (*congenital and infantile hemiatrophy*).

FIG. 58.—Facial hemiatrophy. (After Lichtheim and Borel.)

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See also § 51.

V. Cloudy Swelling and Hydropic Degeneration.

§ 53. The term **cloudy swelling** or *parenchymatous degeneration* or *granular degeneration* is applied to that form of cell-degeneration which is characterized histologically by a swelling and enlargement of the cells due to the formation within the cell-protoplasm of free granules, which according to their microchemical properties (solubility in acetic acid, insolubility in alkalies and ether) are to be regarded as albuminous bodies. The epithelial cells of the kidney and liver (Fig. 59), and the cells of heart-muscle frequently show this degeneration, thereby acquiring a cloudy appearance, as if covered with dust, while at the same time their normal structure (filamentous, granular, alveolar) and form are lost. Thus, for example, in cloudy swelling of the kidney-epithelium the rod-like markings of the protoplasm are lost (Fig. 60, *a*), as are also the cell-processes projecting into the lumen of the tubules. The swollen cells (*b*, *c*, *d*) are larger, more plump, and contain dark granules. This change is to be regarded as a *disorganization of the protoplasm* following an absorption of fluid, and leads to partial separation of

FIG. 59.—Cloudy swelling of liver-cells (scraping from the cut surface of the liver of a man dying of septicæmia, examined in normal salt solution.) × 350.

the solid and liquid constituents of the protoplasm. At the same time the *nucleus swells and undergoes disorganization.*

Recovery is possible at a certain degree, and the cells may be restored to their normal condition. In other cases the cell body is de-

FIG. 60.—Cloudy swelling of kidney epithelium. (Chromic acid, ammonia, glycerin.) *a*, Normal epithelium; *b*, beginning cloudy swelling; *c*, advanced stage of cloudy swelling; *d*, desquamated degenerated epithelium. × 600.

stroyed, breaking up into granular fragments. Fatty degeneration very often accompanies cloudy swelling.

Cloudy swelling may occur in the cells of any of the parenchymatous organs, as the liver, kidneys, or heart, during the course of the majority of the infectious diseases, particularly in scarlet fever, typhoid, smallpox, erysipelas, diphtheria, septicæmia, etc. The affected organs present a cloudy, dull-shining, often gray appearance; in marked cases the organ may appear as if cooked, the blood-content is very slight, the consistency doughy, and the finer details of structure are lost.

It is not improbable that autolytic processes (see paragraph 49) play a rôle in parenchymatous degeneration (*Landsteiner*). *Orgler* regards it as an autolysis accompanied by an increase of the water-content. The granules which become visible and show double refraction he regards as protagon, which, during autolysis, is either preserved because of its slight solubility or during the course of the process is precipitated in the form of granules.

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§ 54. **Hydropic degeneration** is that form of degeneration frequently observed in cells of different kinds, whereby they become swollen through the imbibition of fluid. When epithelial cells undergo this change the cell-contents appear clear, the granules of the protoplasm are pressed farther apart by the fluid, often being crowded into a ring at the periphery of the cell; the cells thus coming to resemble plant-cells to a certain extent. Vacuoles (Fig. 61, *b*)—that is, globules of clear fluid—may often be formed within the cells. The nucleus (*c*) also swells and becomes changed to a large bladder-like vacuole containing clear fluid. In muscles showing hydropic degeneration clear droplets of fluid appear between the fibrillæ, pushing the latter apart (Figs. 62 and 63, *a*, *b*). Through an abundant formation of such drops the muscle fibres may acquire in places an appearance of foam-like bubbles (Fig. 62). At first, the muscle fibres between these drops remain preserved, but finally they undergo fragmentation and liquefaction.

FIG. 61.—Hydropic degeneration of epithelial cells from a carcinoma of the breast. (Müller's fluid, aniline brown.) *a*, Unchanged epithelium; *b*, hydropic cells containing bladder-like drops of fluid [physalides]; *c*, hydropic nuclei; *d*, enlarged nucleoli; *e*, wandering cells. × 300.

Hydropic degeneration of cells may be the result of œdema (Figs. 62 and 63); it occurs also in inflammatory foci (Fig. 41, *d*) and in tumor-cells (Fig. 61). In the case of inflammation the degenerative character of the process is more marked than in the case of œdema; and a complete liquefaction of the cells and nuclei may result. In œdema the cells, in spite of their hydropic condition, may remain alive for a long time.

FIG. 62.—Hydropic degeneration of muscle-fibres from the calf muscle in chronic œdema of the leg. (Flemming's solution, safranin.) × 45.

FIG. 63.—Transverse section of a muscle-bundle showing hydropic degeneration of its fibres. (Müller's fluid, hæmatoxylin.) *a*, Muscle-fibre with small drops of fluid; *b*, muscle-fibre with large drops. × 65.

VI. Fat Deposit and Fatty Degeneration.

§ 55. **Fat**, in a form that can be demonstrated microscopically, is widely distributed throughout the human and animal organism. It appears most prominently in the subcutaneous and subserous tissues and the bone-marrow; in these regions characteristic adipose tissue develops at a certain time during embryonal development or during childhood. Less prominent, and in part visible only on microscopic examination, is the fat present in various glands, also in ganglion-cells, cartilage-cells, leucocytes, surface epithelium, duct epithelium, endothelium, etc.

The fat of adipose tissue occurs in the connective-tissue cells in which it is deposited, in the form of droplets that often become confluent, so that the fully developed fat-cell appears as a fat-spherule surrounded by

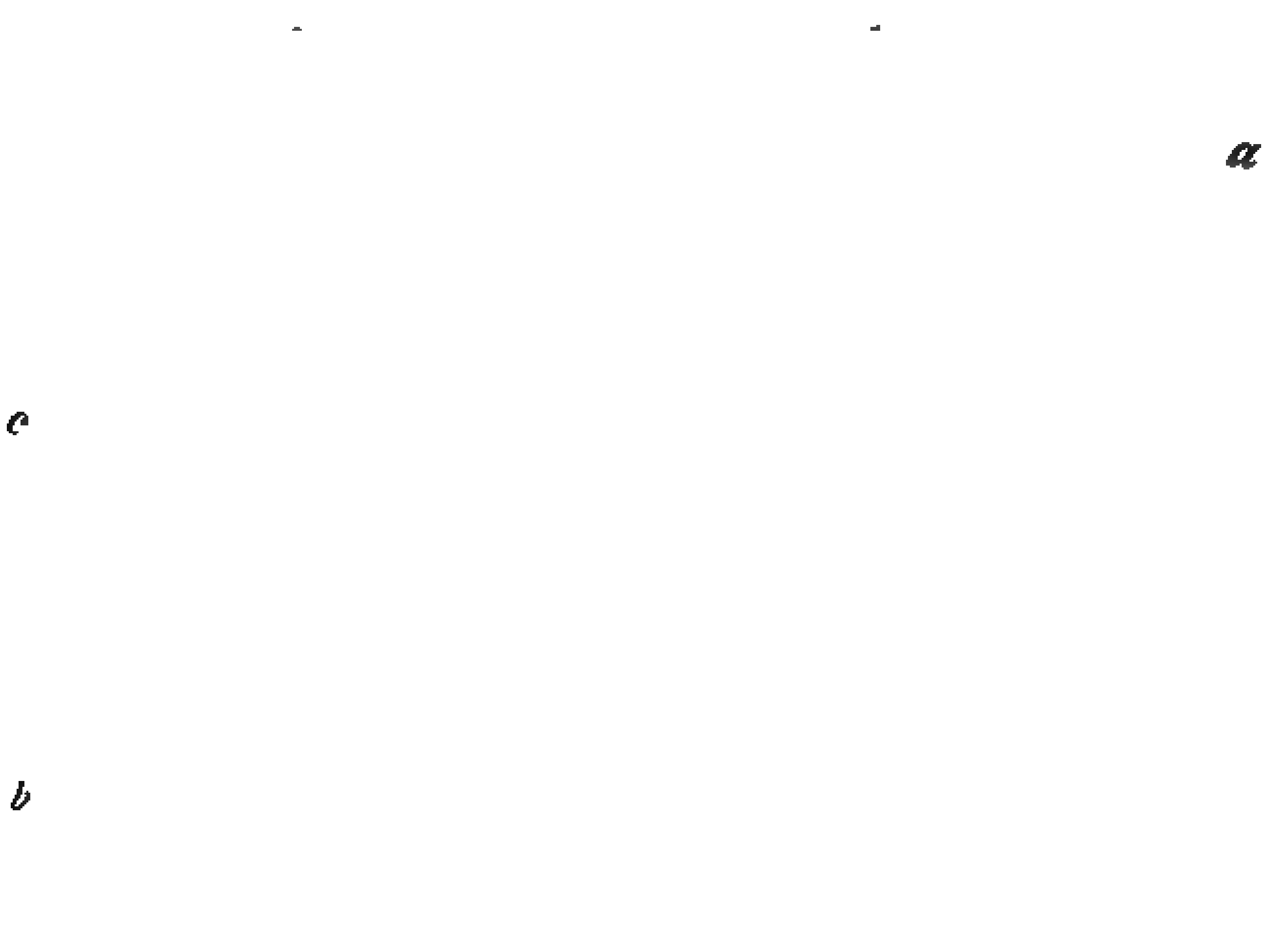

FIG. 64.—Adipose tissue from the panniculus of the heart. (Formalin, hæmatoxylin, and Sudan III.). *a*, Fat tissue; *b*, muscle; *c*, muscle infiltrated with fat tissue. × 40.

a cell-membrane containing a nucleus. In preparations mounted in Canada balsam the fat-drop is represented by a clear vacuole (Fig. 65, *c*). Sudan III. and Scharlach-roth stain fat a yellowish-red (Fig. 64), while treatment with osmic acid, which is reduced by the fat, causes the fat-drops to become blackened (Fig. 67, *c*).

The fat contained in the special adipose tissues of the body is a **stored-up fat** which the organism, in case of necessity, may use for its preservation, and it may, therefore, be designated as a **supply of fat designed for consumption** or **temporary fat.** Its abundance may be regarded as an indication of the condition of nutrition; when this is good the adipose tissues are well developed, in cases of starvation and in chronic marasmus they may vanish entirely. There occurs an **atrophy of fat-tissue,** in which the fat-cells contain only small droplets of fat or

no fat at all, in the latter case reverting to the type of ordinary connective-tissue cells. The atrophic fat-lobules often take on a pale yellow color through the formation of pigment in the cells (*yellow atrophy of adipose-tissue*). Through the collection of fluid between the atrophic fat-cells the fat-tissue (most frequently in the cardiac panniculus) becomes translucent, resembling myxomatous tissue (*serous atrophy of adipose tissue*).

Hypertrophy of adipose tissue leads to the condition known as **obesity, adipositas,** or **lipomatosis.** It is dependent primarily upon an excessive food-supply; but there are frequent individual exceptions to this rule, since in many people an increased formation of panniculus does not take place, no matter how rich the food-supply. Again, an abundant deposit of fat occurs in some individuals when the food-supply

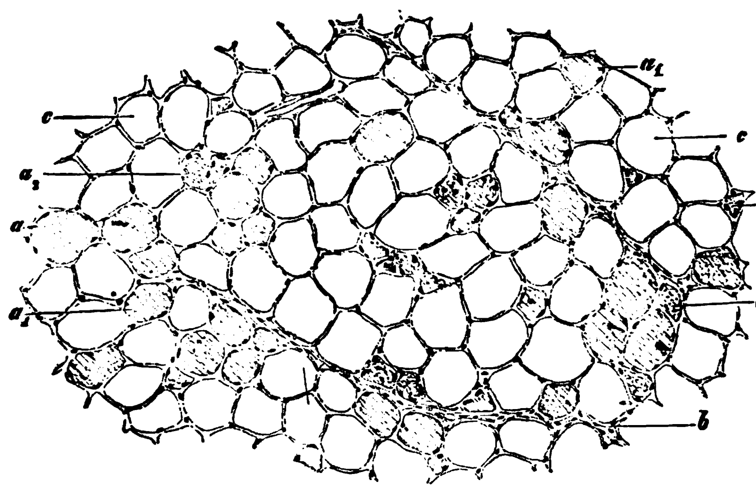

FIG. 65.—Lipomatosis of the calf muscles, associated with atrophy. (Müller's fluid, carmine.) *a*, Transverse section of normal fibre; a_1, of atrophic fibre; a_2, transverse section of sarcolemma tube containing disintegrated contractile substance; *b*, connective tissue; *c*, fat-tissue. × 60.

does not exceed the normal. In such cases the cause of the lipomatosis must be sought in an inability on the part of the organism to destroy the fat brought to it or arising normally within it.

In *general lipomatosis* the deposit of fat takes place first in the normal fat-depots, and then later in places that normally contain no fat, for example, in the connective tissue of the muscles, in the myocardium, and even beneath the endocardium. A *local lipomatosis* may occur in various regions of the body, for example, in an arm, the front of the neck, nape, etc., and leads to deformities of the affected regions resembling elephantiasis. When occurring in circumscribed masses or nodules the condition is classed with the fatty tumors known as *lipomata* (see Lipoma). A local lipomatosis occurs also as a peculiar disease of the muscles in which without the agency of extrinsic causes but as the result of a congenital anlage the muscles, particularly those of the calves of the legs, increase greatly in size (Fig. 65, *c*) through the development of adipose tissue in the perimysium internum. At the same time they become weaker, since many of the muscle-fibres (Fig. 65, *a*, a_1, a_2) may disappear (*atrophia musculorum lipomatosa pseudohypertrophica*). Finally, in other

cases adipose tissue may develop secondarily in places where other tissue has disappeared, for example, within muscles (Fig. 66, *c*) that have become atrophic as the result of disease of the anterior horn of the spinal

FIG. 66.—Spinal muscular atrophy with lipomatosis, in ascending atrophy of the anterior horns of the spinal cord. (Müller's fluid, Bismarck brown.) Section from the calf muscle. *a*, Transverse section of atrophic muscle-fibres; *b*, perimysium; *c*, fat-tissue; *d*, artery; *e*, vein. × 60.

cord or in the case of lymph-glands that in old age have lost, for the greater part, their lymphocytes.

The **fat of the glandular organs** occurs ordinarily in small, even very minute droplets, but in the case of a great abundance of the fat larger droplets may be formed. The sebaceous glands, Meibomian glands, lachrymal glands, and adrenals are especially rich in fat. It oc-

FIG. 67.—Skin with sweat glands, from the sole of the foot. (Osmic acid.) *a*, Thick gland coils with fine fat droplets; *b*, slender gland coils without fat droplets; *c*, fat drops lying about the gland coils. × 390.

curs to a lesser extent in the testicles and ovaries; still less in the salivary glands, thyroid and sweat glands (Fig. 67, *a*). The kidneys have the least fat-content of any of the glands. During the period of functional activity (testicles and ovaries) and in advanced age the fat-content is, in general, somewhat increased. In the testicles and ovaries the fat is

found both in the epithelial cells and in the connective tissue. Further, the fat-content of the glands is very constant and but slightly dependent upon the condition of the general nutrition, so that it does not disappear during starvation (Traina). This glandular fat may then be designated as the **permanent fat** or **intrinsic fat.**

The liver holds an especial position among the glands in so far as fat is concerned. As do the other glands it contains constantly a certain number of fine fat-droplets which do not vanish during starvation. In

FIG. 68.—Fatty liver from a case of pulmonary tuberculosis. (Flemming's solution, safranin.) *a*, Central portion of the liver-lobule; *b*, peripheral zone containing fat; *c*, periportal connective tissue. ×30.

addition there also occurs a temporary storage of fat which, beginning in the periphery of the lobule, extends toward the centre as a progessive filling of the liver-cells with fat-droplets (Fig. 68, *b*); and, finally, the liver-cells may become completely changed into fat-cells, so that the parenchyma acquires a straw-color.

Fatty infiltration of the liver may result from excessive food-supply, but is much more frequently observed in marasmic individuals, particularly in consumptives whose panniculus is atrophic. Inability on the part of the liver to destroy or to give off again the fat brought to it from the intestine or from the fat-depots appears to be the cause of this phenomenon.

Muscle-fibres, surface epithelium, the epithelium of different gland-ducts, cartilage-cells, connective-tissue cells, vascular endothelium, leucocytes, lymphocytes, etc., show a *variable content of fat;* but all contain fat without showing any changes that can be regarded as degenerative in nature. In individual cases it is evident that the fat-content is dependent upon an abundant supply of fat from the intestine or of transportation of fat from the fat-depots, especially in those cases in which the leucocytes or the vascular endothelium (particularly that in the liver) are rich in fat. In still other cases there are definite functional conditions (the muscles) during which a rich supply of fat appears.

The spleen and the lymph-glands, with the exception of the mesenteric glands, to which fat may be brought from the intestine, contain but

little fat; on the other hand, the thymus is relatively rich in fat, particularly at the time of its greatest development.

All **animal fats** are mixtures of olein, palmitin and stearin, that is, of combinations of oleic acid ($C_{18}H_{34}O_2$), stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$) with the trivalent alcohol glycerin ($C_3H_5[OH]_3$) to form neutral esters, the so-called triglycerides. Whether taken in as free fatty acids, as neutral fats, or as soaps, the process of absorption is always the same; they appear constantly in the form of neutral fats in the channels through which absorption takes place.

In close relationship to the body-fats stand the *lecithins* (combinations of each single molecule of glycerin-phosphoric acid with two molecules of fatty acid and the complex of an ammonium base, cholin), the *protagons*, and the *cholesterins*, substances which occur in small amount in the most varied tissues, but abundantly in the myelin of the brain and the peripheral nerves. Cholesterin occurs also in the bile. The breaking-down of all the components of the lecithins containing neutral fat leads first to the formation of fatty-phosphoric acid, which is then split into fatty and glycerin-phosphoric acids.

The fat contained in the human organism is derived primarily from the **food-fat** taken up in the intestine. In the early weeks of life, when the intestine of the nursing infant is still abnormally permeable, the finest fat-droplets are taken up as such and carried through the lymph-stream into the blood. In later life the taking up of unchanged fat through the intestinal epithelium probably takes place to a very slight degree or not at all, that is, the fat is, for the greater part, split up in the intestinal canal, and through the combination of the fatty acids with the alkali present in the intestine there are formed soaps soluble in water, which are absorbed by the epithelium. Even in the intestinal epithelium these soaps are changed into spherules of neutral fat (just as absorbed peptone is again changed into albuminate). The glycerin necessary for this change is absorbed directly from the intestine, where it is present in a free state arising from the splitting of the neutral fats.

FIG. 69.—Fat-granule cells in an anæmic area of softening in the brain. (Marchi's fluid.) *a*, Fat-granule cells; *b*, blood-vessels. × 280.

In the entrance of the fat into the cells of the fat-depots the fat-molecule is again split up and then reconstructed within the cells.

According to *Arnold*, the entrance of fat into the cells is associated in many cases with a certain activity of the plasmosomes, and is therefore connected with the cell-granules, which he regards as the morphological products of the function of the plasmosomes. In the intracellular fat-formation, designated by him as **granular fat-synthesis,** which occurs in leucocytes and lymphocytes, also in endothelial cells, connective-tissue cells, cartilage-cells, epithelial and gland cells, soap is taken into the cells in a soluble form and there undergoes a granular change into fat. The fat-droplets appear at the site of the antecedent granules.

In this manner there arise in part the so-called **fat-granule cells,** leucocytes and lymphocytes closely packed with fat-droplets, that occur frequently in areas of necrosis and inflammation, particularly in the central nervous system (Fig. 69, *a*). According to *Arnold* the uniform size of the fat-droplets speaks in favor of such an origin. Such granule-cells may also be formed through *phagocytosis;* that is, the amœboid cells may take up through their protoplasmic movements fat-droplets lying free in the tissues (in softening of the brain and spinal cord they arise through the disintegration of the medullary sheaths). In the event of such occurrence, chemical and morphological changes in the material taken up are not excluded.

The **carbohydrates** form a second source of fat-formation in the organism, but the chemical processes attending the formation of fat from carbohydrates have not been determined. It is probable that the amount of fat so formed is relatively much less

than the fat taken in as such from the food. It is still a question as to whether fat can be formed in the body from **albumin.** Since many facts speak for the transformation in the animal body of certain groups of the albumin-molecule into glycogen or grape-sugar, the theoretical possibility of the formation of fat from albumin cannot be denied (*Kraus*).

Of the fats and lecithins present in the organism, those containing oleic acid alone reduce osmium tetraoxide to a black osmium hydroxide, so that treatment with osmic acid or Flemming's solution does not show the presence of palmitin and stearin. On the other hand, Sudan III and Scharlach-roth (ponceau) stain all the fats.

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See also § 56.

§ 56. **Fatty degeneration** or *fat-metamorphosis* is *that condition of the cells in which fat-droplets appear in the protoplasm in such a manner as to indicate a change in the chemico-physical cell-structure.* In a part of the cases this change may be inferred from the appearance of the cells, in that fragmentation, disintegration (Fig. 70, *e*, *f*), and separation of the cells from their substratum may be demonstrated.

The views of Virchow were formerly accepted, to the effect that in lipomatosis there occurred a deposit of fat from the blood and tissue-juices; while, on the other hand, in fatty degeneration there took place a formation of fat from the albumin of the degenerating cells. Recent investigations make the latter view doubtful. Although the possibility of a formation of fat from albumin cannot be denied, it has not yet been proved that this is the case in the so-called fatty degeneration of the cells.

In many cases what we call fatty degeneration is only the expression of a *molecular physical deconstitution* of the cells, a fat-metamorphosis, in which the fat contained in the cells in a form that cannot be recognized microscopically is separated out into the form of visible droplets. Therefore, an increase in the actual fat-content of the cell does not occur in fatty degeneration. Renal cells that on microscopical examination show no fat may, nevertheless, contain twenty per cent of fat. Should fatty degeneration occur, so that the fat becomes visible in the form of droplets, the total fat-content is not increased (Rosenfeld, Kraus). A process similar to that taking place within the body occurs during the autolysis of tissue preserved aseptically in the incubator, fat-droplets becoming visible in such tissues (Hansen, Wentscher, Kraus, Müller, and others). When fat as such is

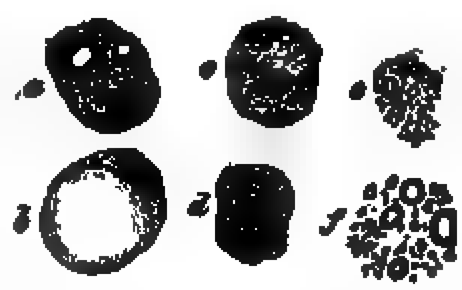

Fig. 70.—Fat-containing liver-cells. *a* and *b*, Fat-infiltration; *c*, *d*, *e*, *f*, fatty degeneration. × 400.

Fig. 71.—Fatty degeneration of the heart-muscle. × 350.

a b e c a b

Fig. 72.—Anæmic and fatty necrosis of the myocardium 85 hours after the closure of a coronary artery. (Flemming's solution, safranin.) *a*, Necrotic; *b*, fatty muscle fibres; *c*, connective tissue with leucocytes containing fat. × 300.

not present in the cells it may arise through a chemical deconstitution of the *lecithin*, *cerebrin*, and *protagons* (myelin) contained in the cells.

A second source of the fat appearing in fatty degeneration is the *fat brought to the affected cells by the blood and tissue-juices*, arising either from

the fat contained in the food or transported from the fat-depots in other tissues. For example, in phosphorus-poisoning a transportation of fat from the panniculus to the liver takes place. It is also probable that the same thing occurs in other intoxications (arsenic, alcohol, chloroform, oleum pulegii). In such cases an increase in the fat-content of the affected organ must result, but this is not always the result of a synthesis of fat, that is, of a formation of higher fatty acids and glycerin and their combination, but is a taking-up of fat that, either as such or as soaps, has been given over to the blood.

FIG. 73. Fatty degeneration, vacuolization, and disorganization of the heart-muscle in a patient dying from pneumonia and nephritis. (Flemming's, safranin.) *a*, Transverse section of normal muscle-cell; *b*, muscle-cell in a state of fatty degeneration; muscle-cells with vacuoles; *d*, disorganized cell. × 400.

In the condition which we call fatty degeneration, the fat appears usually in the form of fine droplets (Figs. 71, 72, *b*, 73, *b*, and 74, *b*), but these may also become confluent to form larger drops (Fig. 75), particularly during the disintegration of the cell (Fig. 70, *f*). The conditions under which the fat of fatty degeneration appears make it probable that the *cells which are the seat of the fatty metamorphosis are still living, but have been injured by extrinsic influences.* In anæmic infarcts of the spleen, kidneys, and heart, the fatty cells (Fig. 72, *b*) are found in the zone of transition between the necrotic (*a*) and the living tissue: that is where the circulation of the blood and lymph is weakened and imperfect, but has not ceased entirely. The appearance of fatty cells in glands (Fig. 70, *c*, *d*, *e*, *f*), in the endothelium of the blood-vessels, or the cells of the heart-muscle (Fig. 73, *b*) occurs in intoxications and infections as the result of cell-injury through toxic action.

FIG. 74.—Marked fatty degeneration (chronic) of the heart-muscle. (Flemming's solution, safranin.) *a*, Normal muscle; *b*, muscle which has undergone fatty degeneration. × 80.

Chronic fatty degeneration of the heart-muscle (Fig. 74, *b*) is seen in valvular lesions, pulmonary emphysema, general anæmia; in the renal

epithelium of consumptives it occurs partly as the result of a diminished supply of oxygen, and partly as the action of toxic substances. Experimental investigations have shown that a long-continued elevation of the body temperature leads to a fatty degeneration of different tissues (heart, kidneys, and liver).

A mild grade of fatty degeneration cannot be seen with the naked eye. The more severe forms of the degeneration give an opaque whitish color to colorless tissues, as, for example, the intima of the blood-vessels and heart-valves, which frequently show patches of fatty metamorphosis. The cortex of a kidney showing fatty degeneration becomes grayish or

FIG. 75.—Fatty degeneration of the renal epithelium, from a case of chronic pulmonary tuberculosis. (Formalin, hæmatoxylin, Sudan III.) × 300.

yellowish in color. In the heart-muscle the yellowish discoloration of fatty degeneration, particularly when the change is localized in small foci (Fig. 74, *b*), stands out very prominently ("tiger-heart").

The questions relating to fatty degeneration have during recent years been the subject of diligent researches, and these have shown that the teaching of Virchow of the formation of fat from the albumin of the body can no longer be accepted. The conclusions resulting from recent investigations are embodied in the text above.

It is not always possible to decide whether the fat present corresponds to a physiological or pathological condition. We can no longer accept the view that fine droplets of fat within the cells signify a pathological condition, since most glands contain small fat-droplets, and other tissues, for example, muscle-fibres, also contain fat-droplets under normal conditions. In favor of a pathological condition speak an increase of fat-content beyond normal limits and a focal occurrence of the fatty change.

In **fat transportation** the fat may appear in the blood in the form of large or small droplets (lipæmia). This is most marked in the case of fat-metastasis due to traumatic lesions of adipose tissue leading to fat-embolism. It may occur, however, under other conditions, as after the abundant absorption of milk or of pure fat from the intestinal canal. Large fat-drops that remain in the vessels disappear slowly, in part associated with an increase of the fat-content of the neighboring tissue. Further, proliferations of the vessel-wall may occur at the site of the embolism, not only after the direct introduction of fat into the blood-vessels, but also after feeding with fat, as in the administration of cod-liver oil (*Wuttig*).

If fasting dogs are fed with mutton-tallow, there is a deposit of mutton-tallow in the fat depots. If they are then poisoned with phosphorus, oleum pulegii, or phloridzin, their livers, which show fatty degeneration as the result of the poisoning, are found to contain mutton-fat in abundance in addition to the animal's own fat (*Rosenfeld*).

According to *Leick* and *Winckler*, the mutton-fat under these conditions is found also in the fatty heart-muscle. In dogs fed with iodopin and afterward poisoned with phosphorus, the iodized fat passes into the liver. In animals devoid of adipose tissue no fatty degeneration occurs in the liver after poisoning with phosphorus or phloridzin (*Rosenfeld*, *Fibiger*).

In the case of *aseptic autolysis of the liver* outside of the body *Waldvogel* has recently made thorough chemical and histological investigations that seem to show that fatty and fat-like products of disintegration may arise *in loco;* and there occurs an increase in those bodies which, related to albumin, have a fat-like (jecorin, lecithin, protagon) or fatty character (fat-acids, neutral fat). In phosphorus-poisoning (*Waldvogel* and *Tintemann*) protagon and jecorin appear as disintegration-products of albumin (the lecithin present is for the greater part transformed into substances which after the acetone precipitation make up the residue of the substances soluble in ether). A similar disintegration of the albumin-molecule occurs in autolysis.

According to *Dietrich*, a formation of fat does not occur in autolysis.

In degenerating cells (kidney, inflamed lung, adrenals, corpus luteum, etc.) doubly refractive droplets similar to fat are found, but they stain only slightly with osmic acid. They are regarded by various authors (Albrecht, Kaiserling, Orgler, etc.) as *myelin*, similar in character to the myelin of the nerve-fibres. It is also probable that protagon appears in this form. Such droplets also appear in the autolysis of cellular tissues.

The kidneys may contain less fat than normal and yet show much fat both to the naked eye and on microscopical examination, as the result of the liberation of the fixed fat in fatty degeneration. The invisible fat is set free and becomes visible. The condition of fatty degeneration, which is a well-established anatomical entity, may be defined, therefore, as an *infiltration of fat from outside into cells degenerating through the influence of poisons or other injurious agents (liver, heart-muscle, pancreas) or as a setting free of the invisible intracellular fat through* autolysis (*kidneys, spleen, muscle*).

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See also § 55.

§ 57. The **fats** which occur in the human body consist almost entirely of a mixture of the glycerin-esters of oleic, palmitic, and stearic acids which are designated *olein*, *palmitin*, and *stearin*. The first is fluid at ordinary temperatures, the second melts at 46°, the third at 53° C. Since the body-fats contain varying proportions of olein, palmitin, and stearin, they vary in consistency and melting-point. If after death the fat-containing tissues of the body are cooled below the melting-point of the contained fat, the stearin and palmitin may separate and form fine stellate or feathery needles (Fig. 76, *b*, *c*, *d*), which are commonly called **margarin needles**, and which, according to the conditions, are found sometimes in fat-cells, at other times free in the tissue-fluids.

Cholesterin occurs in the form of delicate rhombic plates (Fig. 76, *a*), the edges and corners of which are often notched. These may be found wherever there are formed masses of detritus containing fat, arising from degenerating cells or extravasations of blood, as in the diseased tunica vaginalis of the testis, in a dilated sebaceous duct or gland, or in a softened area of degeneration in the wall of a diseased aorta. When the substance in which the cholesterin plates are formed is fluid, these may often be visible to the naked eye as little glistening scales.

Cholesterin ($C_{27}H_{44}O$) is a constant constituent of the bile, and is furnished by the mucous membrane of the gall-bladder and bile-ducts, and held in solution by the bile salts and soaps. It is found also in the medulla of the nerve-fibres, and in small amounts in the blood, where it is held in solution by fats and soaps. According to Burchard traces of cholesterin are found in all the organs.

Cholesterin is insoluble in water, dilute acids, caustic alkalies, and cold alcohol; it is soluble in boiling alcohol, ether, choloroform, and benzol.

When treated with a mixture of five parts of concentrated sulphuric acid and one part of water the edges of cholesterin crystals take on a carmine-red color, which gradually passes into violet. Sulphuric acid

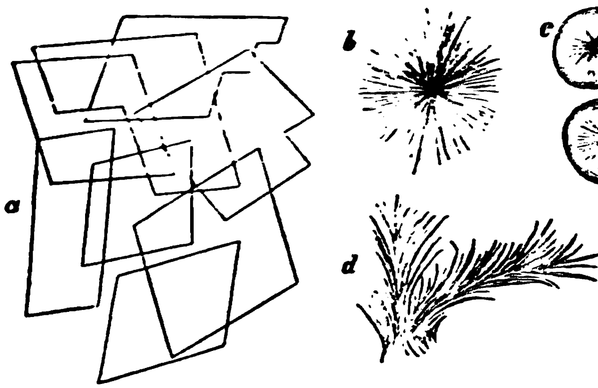

FIG. 78. *a*, Cholesterin plates; *b*, free cluster of margarin needles; *c*, needles enclosed within fat-cells; *d*, grass-like bunch of margarin needles. × 300.

and water mixed in the proportions of three to one give a violet color to the edges of the crystals. Concentrated sulphuric acid containing a trace of iodine colors the crystals violet, blue, green, and red.

The origin of cholesterin is not known with certainty. It is probable that it is an intermediate product in the decomposition of albumin. Corresponding to this view, it is found under those pathological conditions in which albuminous substances break down with the formation of fat.

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VII. The Deposit of Glycogen.

§ 58. **Glycogen** $(C_6H_{10}O_5)^n$ is a carbohydrate which is readily convertible into sugar; and in the body is formed chiefly from the carbohydrates of the food, but may also be formed from albumin and gelatin.

In the tissues of the body, glycogen is found as a *hyaline substance*, most often within the cells, but occasionally in the tissue-spaces. It usually occurs in the form of spherules or lumps of different sizes. In the cells these spherules are most frequently found in the neighborhood of the nucleus.

Glycogen is soluble in water, but the solubility of that found in different tissues varies (Langhans); that found in the liver, kidneys, muscles, and pus-corpuscles is more easily soluble than that of cartilage-cells and surface epithelium. Fixation of the tissue in alcohol renders the glycogen less soluble in water. After death the glycogen of the liver is quickly converted into sugar through the action of a diastatic ferment.

Glycogen becomes brownish-red when treated with iodine. Through a

method given by Best, glycogen may also be stained red with carmine (Fig. 77, *b*, *c*).

Glycogen is present in almost all the tissues of the embryo, also in the fœtal membranes at an early period of development; and in the adult body in the liver-cells, muscles, heart-muscle, cartilage-cells, in the surface epithelium of various organs, in the leucocytes, and in the blood-serum (Gabritschewski). During starvation the glycogen of the liver is diminished, and under pathological conditions may wholly disappear.

Glycogen appears in pathologically increased amount, particularly in diabetes, chiefly in the blood and in the kidneys. The epithelium of the

FIG. 77.—Glycogen degeneration of the renal epithelium in a case of diabetes. (Compare Gierke, l. c.) *a*, Normal tubules; *b*, epithelium with early stage of glycogen deposit; *c*, advanced glycogen deposit with epithelial destruction. × 300.

renal tubules in certain areas contains in part large numbers of small drops (Fig. 77, *b*), and in part also large drops (*c*). Since this deposit leads finally to a destruction of the cells, the condition may be designated as a glycogen degeneration of the cells.

Glycogen occurs also within inflammatory foci (also in infectious proliferations of granulation-tissue [Gierke]), usually first in the polynuclear leucocytes, but also in the so-called epithelioid cells, fibroblasts, and the syncytial giant-cells developing from these, further also in the tissue bordering upon the inflammatory area. Glycogen is also found in many tumors, carcinomata and sarcomata.

It is difficult to determine the **significance of the glycogen appearing under pathological conditions.** Since glycogen is abundant in embryonal tissues and in quickly growing tumors, *Brault* is of the opinion that its appearance is a sign of an increased proliferative cell activity; but the presence of glycogen in large amounts in pus-cells does not agree with this theory. Moreover, in tumors it is not found in the regions of most active cell proliferation. According to *Gierke*, glycogen appears by preference in those tissues deprived to a certain extent of the circulation. A certain

parallel exists between the occurrence of fatty degeneration and glycogen deposit. Both changes are found, for example, in inflammatory foci and at the edge of necrotic areas. In both cases degenerating cells are present that are able to take up both fat and glycogen, but can no longer change them.

According to *Wolff*, the leucocytes circulating in the normal blood also contain glycogen, but this glycogen is very easily soluble, and therefore difficult to demonstrate. In many infections and inflammatory exudates the glycogen of the leucocytes becomes less soluble and can therefore be more easily demonstrated.

The iodophile hyaline substance contained in the tissues is not a pure glycogen, but is most probably a combination of glycogen with an albumin-like substance. To avoid the solution in water of glycogen in fresh preparations, a syrupy solution of iodine in gum (*Ehrlich*) or iodine-glycerin (*Barfurth*) may be used in this investigation. Sections of tissues hardened in alcohol are best treated (*Langhans*) with a dilute tincture of iodine (1 part tincture iodine to 4 parts absolute alcohol), and then cleared in oleum origani in which the reaction is preserved for a long time. The reaction is also preserved for a long time in hard Canada balsam. For the staining of glycogen with carmine, *Best* gives the following method: the sections are first stained with hæmatoxylin and are then stained for three-fourths to one hour in a mixture of two parts of a solution of carmine (carmine 1.0 grm., ammonium chlorate 2.0 grms., lithium carbonate 0.5 grm., aq. dest. 50 grms., brought to a boiling-point, after which there is added 20 c.c. of liq. ammon. caust.), 3 parts of liq. am. caust. and 6 parts of methyl alcohol. They are then decolorized for a few minutes in a mixture of 2 parts methyl alcohol, 4 parts absolute alcohol, and 5 parts water, and finally mounted in Canada balsam.

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VIII. Mucous Degeneration.

§ 59. **Mucous degeneration** has its physiological prototype in the production of mucus by the mucous membranes and mucous glands, and in the formation of mucus in the connective tissue of the umbilical cord, tendons, bursæ, and synovial membranes. In the umbilical cord the mucus occurs as a jelly-like matrix; in the joints, bursæ, and tendon-sheaths it forms a clear, stringy fluid.

In the epithelium of the mucous membranes the mucus appears first in the goblet-cells (Fig. 78, *a*), forming a clear substance which stains with hæmatoxylin. In mucous glands, during the process of mucus formation, the epithelial cells swell, their central portions become clear, and the granules of the protoplasm are reduced to small groups or strands. The so-called mucous corpuscles of the salivary secretion, which are characterized by glassy, transparent contents and vibrating protoplasmic granules, are round cells which have undergone mucous degeneration.

The mucus formed from the protoplasm of the cells may be discharged, and the cells remain intact, or in other cases they may be destroyed.

FIG. 78.—Formation of mucus within the epithelial cells of an adenomatous polyp of the small intestine. (Alcohol, hæmatoxylin.) *a*, Epithelium with dark-stained (hæmatoxylin) drops of mucus within the cells; *b*, free mucus; *c*, leucocytes in the epithelium. × 300.

Mucus is produced in the same way under pathological conditions as under normal (Fig. 78, *a*). In catarrh of the mucous membranes there is an increased formation of mucus by the cells of the superficial epithelium as well as those of the glands. In addition the pus-corpuscles may also undergo mucous degeneration, the mucin being formed from the nuclein of the nuclei (Kossel). In mucous membranes covered with cylindrical cells the number of goblet-cells is increased, and in the secretion there are found cells which have undergone complete mucous degeneration—that is, they have been converted into glassy masses containing few granules. Other cells contain the mucus in the form of drops of varying size.

The epithelium of pathological tissues may also undergo a mucous degeneration, in a manner similar to that occurring in normal tissues. Thus the epithelial lining of cysts of the ovary and of intestinal tumors may often contain numerous goblet-cells (Fig. 79, *a*), and cells which have undergone total mucous degeneration (*b*). In the so-called gelatinous or mucoid carcinoma (colloid carcinoma) a large part of the epithelial cells suffer a mucous metamorphosis.

Of the *connective tissues*, which may suffer a mucous degeneration and thereby acquire a gelatinous, transparent appearance, may be mentioned fibrous connective tissue, also cartilage, bone, adipose tissue, bone-marrow, and sarcomatous tissue. In these tissues it is chiefly the ground-

substance (Fig. 80, *b*) which undergoes mucous change and is converted into a homogeneous, structureless mass. The cells may remain unchanged, or may become fatty, or also undergo mucous degeneration. In the last event the entire tissue ultimately forms a hyaline mass, in

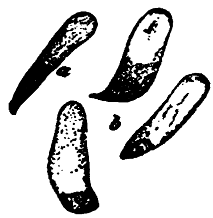

FIG. 79.

FIG. 80.

FIG. 79.—Epithelial cells which have undergone mucous degeneration, from a cystadenoma of the ovary. *a*, Cells showing slight change; *b*, cells showing marked degree of mucous change. × 400.

FIG. 80.—Mucous degeneration of the connective tissue of the aortic valves (osmic acid, glycerin). *a*, Fibrous tissue; *b*, myxomatous tissue. × 350.

which only scattered fibres of connective tissue, or single cells or groups of cells are left to suggest the original tissue.

The stringy, or gelatinous material, which results from mucous degeneration, does not represent a single chemical substance; in it there may be found different varieties of mucins as well as of pseudomucins.

The **mucins** (submaxillary, intestinal, and tendon mucin) are nitrogenous substances somewhat resembling albumin. They dissolve or swell up in water forming a stringy, mucous fluid, from which they may be precipitated in a stringy form by means of alcohol or acetic acid; but differ from the true albumins in the fact that the precipitate is not redissolved in an excess of the acid. The precipitated mucins are soluble in neutral salt-solutions, caustic alkalies, and alkaline carbonates; and are gradually converted into alkali-albuminates in case of solution by the last named.

All mucins contain nitrogen and sulphur; their content in carbon, oxygen, nitrogen, and sulphur varies in the different forms.

Pseudomucin also dissolves in water, forming a gelatinous fluid, from which it may be precipitated in stringy masses by alcohol. The precipitate redissolves in water. Solutions of pseudomucin are not precipitated by acetic acid.

Pseudomucin is found particularly in ovarian cystomata, and is the cause of the gelatinous character of the cyst-contents. It is produced by the epithelium of these tumors (Fig. 79); and in its formation the same changes take place in the cells, as in the formation of mucin from epithelium. In all probability the mucous substance present in gelatinous carcinomata is a body closely related to pseudomucin or metalbumin—that is, there are different varieties of pseudomucin (Pfannenstiel), of which the two mentioned are examples.

Through proper treatment the *mucins* may be split into a carbohydrate, animal gum (*Landwehr, Hammarsten*), and mucin may therefore be designated a glycoproteid (*Pfannenstiel*). The *pseudomucins* when treated with dilute mineral acids likewise split off a carbohydrate which reduces copper sulphate in alkaline solution (*Pfannenstiel*).

The mucin-like substances, precipitable by acetic acid, which occur in the *synovial fluid*, differ, according to *Salkowski*, from nucleoalbumin in the absence of phosphorus. From ordinary mucin they are distinguished by their different behavior with mineral acids; when boiled with dilute hydrochloric acid no reducing substance is obtained.

Mitjukoff has obtained from the gelatinous contents of an ovarian cyst a mucin-like substance which he has named *paramucin*. It differs from pseudomucin chiefly in the fact that without previous boiling with dilute acids it reduces copper oxide in an alkaline solution.

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IX. Formation of Epithelial Colloid and Epithelial Hyaline Concretions.

§ 60. The **epithelial formation of colloid** is a process closely related to the epithelial production of mucus; it consists partly in a secretion of

FIG. 81. FIG. 82.

FIG. 81.—Colloid in enlarged thyroid gland. (Alcohol, hæmatoxylin.) *a*, Follicle filled with cells; *b*, follicle showing lumen; *c*, masses of colloid; *d*, capillary; *e*, connective-tissue septum with artery. × 60.

FIG. 82.—Secretion of colloid in the thyroid. (After Bozzi.) *a*, Colloid; *b*, secreting cells with granules.

colloid by gland-cells, and partly in a conversion of entire cells into colloid. Physiologically, colloid is found in the thyroid (Fig. 82), where it

appears in the form of *hyaline, rather firm, colorless, or slightly colored, jelly-like masses*, which in the first place fill the follicles (c), but from these may extend into the lymph-vessels of the thyroid. *Pathological collections of colloid* occur both in normal gland-tissue and in newly-formed glandular-tissue of pathological nature. The accumulation causes a more or less marked distention of the follicles, and thereby leads to an enlargement of the affected gland, which is known as colloid goitre or bronchocele.

FIG. 83.—Dilated urinary tubules filled with colloid. (Müller's fluid, hæmatoxylin, and eosin.) × 250.

The typical secretion of colloid is characterized by the formation of homogeneous granules and spherules in that portion of the epithelial cells next to the lumen of the follicle (Fig. 82). Some of the cells may be completely filled with these granules. In excessive and atypical formation desquamated cells may become converted into the hyaline substance of colloid.

The colloid of the thyroid is found on microscopical examination to be *homogeneous;* and according to its appearance it may be designated **epithelial hyalin.** As a rule it incloses no cellular elements, but degenerating cells may be found in it. Alcohol and acetic acid cause no clouding, or precipitation in the form of threads, as happens in the case of mucin when so treated. By means of Van Gieson's staining method the colloid is stained orange-red, while the connective tissue takes a fuchsin-red. It must be noted that the contents of the thyroid follicles, which are designated colloid, are not always of the same character. At one time the substance is firm, at another soft or even fluid, or at least is readily soluble in water. In preparations fixed in alcohol a granulation or cleavage may be caused by contraction; and the staining reactions are not always the same.

FIG. 84.—Colloid concretions in the cystic dilated tubules of the parovarium. (Formalin, Van Gieson's stain.) a, b, Gland-tubules of the parovarium; c, cysts containing colloid concretions (d). × 80.

The chemical nature of the thyroid colloid is not fully known, and it is probable that the contents of the follicles are of variable composition. It is most probably an albuminoid body which is combined with iodothyrin, the active principle of the thyroid gland.

Epithelial hyalin is also found in the glands of the hypophysis cerebri, in the urinary tubules of diseased kidneys (Fig. 83), in the prostate (Fig. 85, *d*), in cysts of the parovarium (Fig. 84, *d*), in the glands of the stomach, and more rarely in other glands. In the last-named organs the hyalin occurs in the form of a uniformly homogeneous mass completely

FIG. 85.—Section from a hypertrophic prostate with concretions. (Müller's fluid, hæmatoxylin, and eosin.) *a*, Stroma; *b*, glands; *c*, dilated glands; *d*, concretions. × 45.

filling the gland-lumen, or often as **hyaline,** in part **laminated concretions** (Fig. 84, *d*, and Fig. 85, *d*) of more or less firm consistency.

It must not be assumed that the last-named formations are identical in their chemical composition with thyroid colloid. The only thing which they possess in common is this: they both represent *transformed protoplasm of gland-cells*—a substance which is *hyaline*, possesses a certain firmness, and *does not react to chemical reagents in the same manner as does mucin.* These concretions may also undergo changes which necessitate, on their part, a different behavior toward microchemical reactions. This is particularly true of the prostatic concretions, which not infrequently show, when treated with iodine, a reaction that has been taken as evidence that they are composed of amyloid material (see § 63). It may be proved, both in the case of prostatic concretions and of renal colloid, that they represent cell-material which has become changed into hyaline substance. In the case of renal colloid, however, it is only under especial conditions that the participation in its formation of albumin derived from the glomeruli may be excluded.

Colloid is a **collective term** which is applied to a great variety of formations that possess only certain physical attributes in common. There is a very great difference of opinion among authors as to the application of the term. Under colloid degeneration, for example, *von Recklinghausen* places mucous, amyloid, and hyaline degenerations: including under the last-named epithelial colloid-formation, hyaline degeneration of connective tissue, as well as hyaline coagulation-necroses and hyaline thrombi. *Marchand* gives the term a more limited application, but includes under colloid certain forms of epithelial mucin-formation (particularly in tumors), and also hyaline formations in connective tissue. Inasmuch as colloid is not a definite chemical entity, and as its staining-reactions do not differentiate it sharply from other hyaline substances, it seems to me most expedient to apply the term only to those hyaline products of epithe-

lium which do not possess the characteristics of mucin. I have, therefore, also classified as colloid those epithelial concretions which on account of their reaction with iodine (brown or blue color when treated with dilute iodine solutions) have hitherto been regarded as amyloid bodies. If objection is made to the classification of these formations as colloid, they may be placed under the heading of **epithelial hyalin.**

As epithelial hyalin (keratohyalin?) may be classed also the *hyaline granules and spherules* described by *Russel*, *Klein*, and others, and which are found especially in cancer cells. They stain intensely with fuchsin, and also with Gram's method or with Weigert's fibrin stain. It should be noted further that similar bodies of varying size and form have been observed in the epithelium during the development of a vaccination pustule (*Hückel*), and have been by many regarded as parasites.

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X. The Pathological Cornification of Epithelium.

§ 61. The **cornification of the surface epithelium** over the entire skin is a physiological process, characterized essentially by the fact that the cells in the outer strata of the prickle layer of the *stratum germinativum* undergo a horny change. This cornification takes place first at the periphery of the cells and in the processes binding the cells together, while at the same time the inner portions of the cell and the nucleus shrink, so that the cells become changed into thin, flat, horny scales. This horny substance or *keratin* is a very resistant modified albuminoid body of homogeneous composition, and is capable of resisting digestion by the gastric or pancreatic juices.

As accompanying phenomena of cornification there appear in the cells of the prickle layer peculiar hyaline granules and spherules resembling colloid, which stain intensely with nuclear stains and are known as *keratohyalin* (Waldeyer). In those areas of the skin possessing a thick horny layer, there is formed a sharply limited layer of such keratohyalin-containing cells; this layer is known as the *stratum granulosum*. In those places where the horny layer is thin, the stratum granulosum is imperfectly developed and exhibits breaks of continuity.

Pathological cornification may occur, in the first place, as a widespread or localized increase of the horny layer, resulting in a condition of *hypertrophy of the horny layer of the epidermis* (see Chapter VI., § 76),

or *hyperkeratosis*. This phenomenon may be primary—that is, due to intrinsic causes inherent in the anlage of the skin (ichthyosis, lichen pilaris)—or may be acquired as the result of external influences, mechanical lesions, infections and inflammations (callosities, corns). Further, there may occur disturbances in the process of cornification of the skin, so that certain pathological manifestations recognizable by the naked eye may make their appearance, such as desquamation of the skin. Such changes are included under the term *parakeratoses*. They occur especially as sequelæ or concomitant phenomena of infections of the epidermis, and of inflammations of the corium and papillary body, sometimes without any recognizable cause; and in these cases either the process of cornification or of the formation of keratohyalin, or both, is disturbed.

Finally, *pathological cornification often occurs in regions where normally it either does not occur at all or but to a slight extent*. In the skin the cornification may extend to the ducts of the sebaceous glands and to the hair-follicles (ichthyosis) or to the sweat-glands (porokeratosis). Further, pathological cornification occurs not infrequently in the mucous membrane of the mouth, giving rise to white thickenings of the epithelium or to hair-like formations (hairy tongue). Horny change may be observed also in the mucous membrane of the middle ear, in the mastoid cells, in the descending urinary passages, and in these places it may lead to the formation of shining white scales (*formation of cholesteatomata*).

Cornification of cancer cells is very frequently seen, particularly in cancers of the skin, in which the horny scales are found usually in the form of round masses resembling onions or pearls. Similar horny products are also found in *cholesteatomata of the pia and brain*.

The pathological formation of horny substance in the mucous membranes or in tumors takes place either simply through cornification of the cell-membranes with contraction of the cell, or it may be combined with the formation of keratohyalin as in the case of typical cornification. The formation of keratohyalin and the cornification of epithelial cells often occur irregularly distributed, particularly in cancers.

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XI. Amyloid Degeneration and the Amyloid Concretions.

§ 62. **Amyloid degeneration is a peculiar degeneration of the connective tissue of the blood-vessels,** characterized by a *deposit of an albuminoid substance* (*amyloid*) in the affected part, so that the tissue increases in mass and at the same time acquires a peculiar, *glassy, homogeneous appearance*. The degeneration may occur in almost all the organs of the body; but is especially frequent in the spleen, liver, kidneys, intestine, stomach, adrenals, pancreas, and the lymph-glands. It is more rarely observed in adipose tissue, thyroid gland, aorta, heart, muscles, ovaries, uterus, and in the urinary passages.

Extensive deposits of amyloid may be recognized by the naked eye, as the affected parts present a translucent appearance resembling bacon (*lardaceous degeneration*).

In the *spleen* the change occurs most frequently in the follicles, which in a certain stage of the degeneration may become converted into homogeneous, translucent bodies (Fig. 86, *b*) resembling grains of boiled sago, wherefore this form of amyloid spleen is known as *sago spleen*. When the amyloid change occurs throughout the spleen-pulp it may be recognized on the cut surface of the organ as more or less distinct spots or streaks. Ultimately the greater part of the substance of the spleen may become affected. The spleen is thus enlarged, its consistency becomes

FIG. 86.—Amyloid degeneration of the splenic follicles and neighboring tissue. (Müller's fluid, hæmatoxylin, and eosin.) *a*, Transverse section of splenic artery; *b*, amyloid areas; *c*, pulp; *d*, trabeculæ. × 30.

very hard, and the organ under certain conditions may be completely transformed into a bacon-like substance (*lardaceous spleen*).

The *liver*, in cases of well-marked amyloid degeneration, is increased in size and of a firmer consistency. On section, the liver-tissue is found to be replaced to a greater or less extent by translucent, lardaceous masses, between which the remains of the liver-tissue appear as brownish or yellowish (from abundance of contained fat) areas.

The *kidney*, in cases of extensive amyloid change, is likewise enlarged and hardened, and on section shows hyaline, lardaceous spots and streaks of firm consistency. More frequently there is found a white, fatty, swollen, or normal-sized kidney, in which only here and there may be seen small hyaline granules or streaks, or the presence of amyloid may be recognized only after the tissues have been treated with iodine.

In the intestine and lymph-glands the degeneration usually cannot

FIG. 87.—Section from an amyloid liver, treated with iodine solution. × 35.

be recognized without the aid of the microscope and chemical reagents; and the same thing is true in regard to the other organs which are more rarely affected, such as adipose tissue, heart-muscle, the great blood-vessels, the thyroid gland, etc.

The substance which is deposited in amyloid degeneration forms chiefly **shining, homogeneous masses,** which exhibit a *characteristic reaction with iodine as well as with various aniline dyes. Iodine* dissolved in water, or better in a solution of potassium iodide, and poured over the affected tissue, stains the amyloid substance a *dark brownish-red* (mahogany brown). In thin sections, under the microscope, the amyloid appears a bright *brown-red* (Fig. 87, *b*) while the remaining tissue is of a straw-yellow color (*a*).

In marked amyloid degeneration, when the tissues are of a wooden hardness, the iodine reaction sometimes gives a *blue* or *green color*. Preparations which have been changed to a mahogany brown through the action of iodine become still deeper brown when treated with dilute sulphuric acid or with a solution of zinc chloride, or they may become bright red, violet, blue, or green. This reaction is, however, imperfect in the majority of cases.

Methyl violet stains amyloid a *ruby red* (Fig. 88, *a, b*), while the normal tissue takes a blue or dark blue-violet.

Because of the peculiar reaction with iodine, Virchow was led to re-

garded the amyloid substance as a non-nitrogenous body closely related to cellulose or starch, inasmuch as cellulose when treated with iodine and concentrated sulphuric acid becomes bright blue, and starch similarly treated gives an ultramarine color. Virchow accordingly gave the name amyloid to the newly discovered substance. Several years later Friedreich and Kekulé showed that amyloid is a nitrogenous body of an albuminous nature. According to the investigations of Krawkow amyloid is a firm combination of chondroitin-sulphuric acid with an albumin.

The peculiar reactions of amyloid enable us to detect its presence in the tissues when it is present in such small amounts as to be otherwise practically invisible. In the microscopic examination of fresh preparations care should be taken to wash out the blood from the piece of tissue, since the color resulting from the combination of the blood and the iodine may be deceptive.

Amyloid is very resistant to acids and alkalies. Alcohol and chromic acid do not affect it; and it is also very resistant to putrefactive changes.

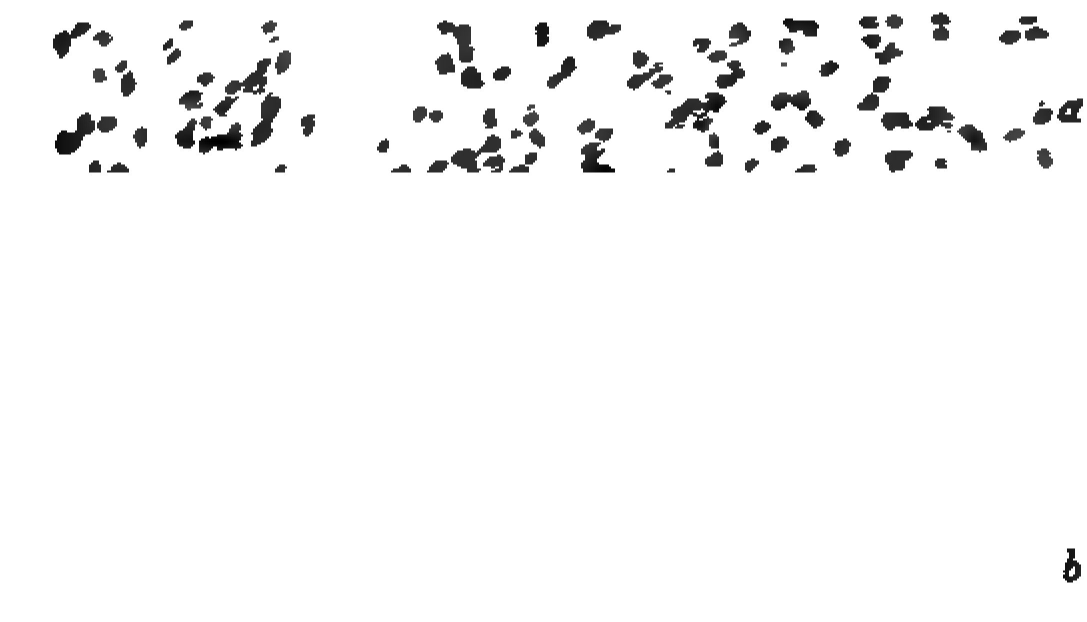

Fig. 88.—Amyloid degeneration of the splenic follicles and pulp. (Alcohol, methyl violet, hydrochloric acid.) a, Follicle showing marked degeneration; b, pulp showing beginning degeneration. × 300.

Amyloid is deposited *in the ground-substance of the connective tissue of the blood-vessels, especially in the walls of the small vessels.* Living cells are not affected. In the connective tissue the amyloid substance appears first between the fibrillæ.

In the acini of the liver the amyloid is found along the capillaries. The endothelium (Fig. 89, *c*) is covered on its outer side by a thick layer of a homogeneous, glassy substance, which in part may be broken up through numerous clefts into lumpy masses (*c*) of amyloid material. The liver cells between the amyloid masses are either intact (*a*) or compressed (*b*), or already atrophic, or may have wholly disappeared. They very often contain fat. The afferent blood-vessels of the liver, particularly the media of the arteries, may also show amyloid deposits.

In the kidneys (Fig. 90) the amyloid is found particularly in the vessel-walls. The capillaries of the glomeruli (*b*) may be greatly thickened and homogeneous; likewise the arteries (*i*), the veins, and the capillaries (*k*) of other parts of the renal parenchyma may show amyloid

deposits. In the intestinal mucosa the deposit is also found particularly in the walls of the blood-vessels.

In fat-tissue, which is occasionally extensively involved, the amyloid substance is found partly in the vessel-walls, and partly in the connective tissue, and the membranous sheath of the fat-cells may be entirely converted into a hyaline mass. In the spleen the connective-tissue trabeculæ (Fig. 88, *a*, *b*) and the vessel-walls are especially likely to be affected, and may suffer a marked thickening (*b*). In striped muscle the perimysium internum and the sarcolemma are involved. In glandular organs possessing a tunica propria, as, for example, the mucous

FIG. 89.—Amyloid degeneration of the liver. (Alcohol. Van Gieson's.) *a*, Liver-cells, in part containing fat: *b*, compressed liver-cells; *c*, amyloid. × 250.

glands and the kidneys, this membrane may become affected and greatly thickened.

The **results** of amyloid degeneration upon the functions and vitality of the affected organ are shown, through anatomical investigation, most prominently in the marked *change of structure* on the one hand, and on the other hand in the associated *degeneration* and the *disappearance of the cellular elements*. Amyloid disease is eminently degenerative in character. The connective tissue itself is permanently changed, as the practically insoluble amyloid is never removed from it.

The deposit of amyloid substance in the tissues of the blood-vessels leads to a very marked thickening of their walls, and to a narrowing or even obliteration of their lumina (Fig. 90, *b*), and in this way to a permanent disturbance of circulation. The amyloid masses may compress neighboring epithelial structures (Fig. 89) and cause them to atrophy. Often there is associated a fatty degeneration of the epithelium (Fig. 90, *e*, *f*), particularly in the kidneys; but this change is not to be referred wholly to the disturbances of circulation caused by the amyloid deposit. It is more likely that the fatty degeneration, at least in part, is a pathological process running parallel with the amyloid disease, and caused by the same conditions producing the latter. Consequently, in some

cases the amyloid change may be slight, while the fatty degeneration very marked.

In the spleen and lymph-glands the lymphoid cells lying in t meshes of the thickened reticulum (Fig. 88, *a*) disappear as the result atrophy and fatty degeneration. In muscles the contractile substan diminishes in proportion to the increase of the amyloid deposit in co nective tissue.

Amyloid deposit is usually a sequela of cachexia due to *chronic ulc ative tuberculosis* of different organs, *chronic suppuration* (for example, the bones), *syphilis*, or *chronic dysentery*. In the cachexia of carcinor it is but rarely observed. In rare cases the degeneration occurs witho being associated with any of the above-mentioned diseases.

According to investigations by Czerny, Krawkow, Lubarsch, Davi sohn, Maximow, Nowak, Petrone, and Schepilewsky amyloid may produced experimentally in the spleen, liver, kidneys, and intestines various animals, rabbits, chickens, doves, mice, and dogs, through t

FIG. 90.—Section of an amyloid kidney. (Müller's fluid, osmic acid, methyl violet.) *a*, Normal vas lar loops; *b*, amyloid vascular loops; *c*, fatty glomerular epithelium; c_1, fatty capsular epithelium; *d*, f drops lying against the outer surface of the capillary walls; *e*, fatty epithelium *in situ*; *f*, desquamat and fatty epithelium; *g*, hyaline coagula (cast); *h*, transverse section of a cast composed of fat-drops; amyloid artery; *k*, amyloid capillary; *l*, cellular infiltration of the connective tissue; *m*, round cells wit the tubules. × 300.

production of suppurations lasting several weeks. Amyloid may d velop also in horses that are inoculated with diphtheria bacilli. Suppur tive processes caused by staphylococci and oil of turpentine appear particular to favor the formation of amyloid. In a number of cases am loid was also successfully produced through injections of decompos bouillon, dead cultures of staphylococci, rennet-ferment, and pancreat (Schepilewsky), when the inflammation produced by these agencies r a somewhat chronic course. Krawkow observed the beginning of am loid formation after three days, Nowak after eight days.

The *origin of the amyloid substance* has not yet been definitely dete mined. The results of experimental investigation vary greatly, the d generation being often absent in cases of chronic suppuration (partic

larly in dogs). It is probable that the blood brings to the tissues some substance which is changed into amyloid at the site of deposit. It has been many times shown that as the *antecedent of amyloid* there is found *a hyaline substance* in the tissues, which does not give the amyloid reactions. Similar observations have occasionally been made in man. The material from which amyloid arises is formed, perhaps, by disintegrating pus-cells or tissue-cells at the seat of the primary disease and thence enters the blood-stream.

According to *Krawkow*, there are found normally in the wall of the horse's aorta, in the ligamentum nuchæ of cattle, in the stroma of the spleen of calves, and in the mucous membrane of the stomach, combinations of chondroitin-sulphuric acid which are closely related to amyloid. According to *Neuberg*, amyloid proper is a basic albumin in the process of metamorphosis combined with chondroitin-sulphuric acid. From this last-named combination the basic albumin body may be easily differentiated chemically.

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§ 63. The form of amyloid degeneration just considered is a disease which usually appears as a multiple affection of several organs, or, if confined to a single organ, appears as a diffuse change extending throughout the whole organ. There is, however, a localized form of amyloid deposit, appearing either as a *local amyloid infiltration of the tissues* or in the *form of free concretions.*

The **local amyloid infiltrations** occur in part in very cellular granulations (conjunctiva) and in tissues showing chronic inflammatory processes; and in part in scars and in hyperplastic proliferations of connective tissue. They are also found occasionally in tumors in which other retrograde changes have begun. In certain cases only small deposits are found in the affected tissues, usually in the vessel-walls. In other cases larger nodules consisting almost wholly of amyloid may be formed, and these may acquire a wooden hardness.

Here also the *amyloid substance is deposited in the ground-substance of the tissue;* but it has been claimed by some authors (Rählmann) that the cells of the tissue may acquire a hyaline appearance and give the amyloid reactions.

Such local formations of amyloid have been found in the inflamed conjunctiva, in syphilitic scars of the liver, tongue, and larynx, in inflamed lymph-glands, in the urinary bladder, ulcers of the leg, and in tumors of the larynx and stomach. **Tumor-like nodules of amyloid** also occur in the conjunctiva, tongue, larynx, lymph-glands, and trachea under conditions in which it is impossible to establish any relationship between them and inflammatory processes, and where besides the hyaline masses there is but little normal connective tissue present. According to Burow, Manasse, von Schrötter, Zahn, and others, such nodules may arise also from connective-tissue tumors.

Free amyloid concretions or **corpora amylacea** occur most frequently in the tissues of the central nervous system, especially in the substance of the spinal cord, and in the ependyma of the ventricle. They are found also in the prostate. In the nervous system they appear as small (Fig. 91, *c*), dull-shining, mostly homogeneous bodies, more rarely consisting of a nucleus and an outer shell (Redlich); in the prostate they form larger (Fig. 91, *a*) bodies which usually show a distinct stratification. Corpora amylacea have also been found in carcinomata (Wagner, Langhans), and have been repeatedly observed in the lung, where they occur in inflammatory areas, hæmorrhagic extravasations (*b*), and in emphysema.

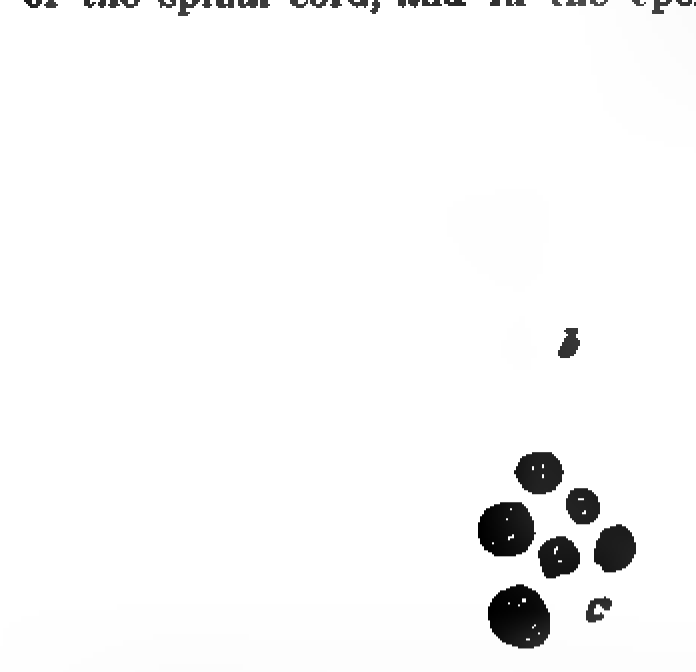

FIG. 91.—Corpora amylacea. *a*, Laminated prostatic concretions. × 200. *b*, Corpus amylaceum from an old hæmorrhagic infarct of the lung, with hæmatoidin crystals in its nucleus. × 200. *c*, Corpora amylacea from the spinal cord. × 400.

The *local deposits of amyloid and the free amyloid concretions cannot be regarded as being wholly of the same nature as the progressive amyloid degeneration of connective tissue.* Some of them indeed give characteristic amyloid reactions, and the corpora amylacea of the nervous system, in particular, become blue or brownish-

violet when treated with iodine and sulphuric acid. But, in the case of these bodies, we have to do with formations which are dependent essentially upon local conditions for their origin; and which are derived in part from epithelium, and in part from connective-tissue cells. They are, therefore, to be regarded partly as modified epithelial hyalin (§ 60), and partly as modified connective-tissue hyalin (§ 65). The prostatic concretions are formed through the fusion of masses of degenerating epithelial cells or of fragments of the same (epithelial colloid, § 60); and the similar bodies found in the lungs and in tumors are composed essentially of the products of disintegrated cells, though in part also of albumin derived from the blood. The corpora amylacea of the nervous system arise probably from fragments of swollen axis-cylinders to which, perhaps, remains of the changed medullary sheath still cling.

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XII. Hyaline Degeneration of Connective Tissue and the Hyaline Products of Connective-tissue Cells.

§ 64. Under the head of **hyaline degeneration of connective tissue** may be grouped those changes in which the *fibrous ground-substance of the connective tissue of the blood-vessels acquires a hyaline character without giving the specific reactions of amyloid* (Fig. 92). The change may involve normal connective tissue (Fig. 92), or that altered by inflammation, as well as the newly formed connective tissue of inflammatory new-growths and of tumors. It is dependent partly upon local and partly upon general disturbances of circulation. Hyaline degeneration is found most often in the connective tissue of the thyroid (Fig. 92, *b*); the valvular endocardium; intima of the arteries; the entire wall of the smaller vessels, particularly of the brain and spinal cord; the lymph-glands (Fig. 94, *a*, *b*); glomeruli of the kidney; the connective tissue and blood-vessels of connective tissue tumors of the dura mater (psammoma), parotid, and submaxillary glands (angiosarcoma); the connective tissue of corneal scars; the peripheral portions of tuberculous nodules; the connective tissue of tuberculous tendon-sheaths and bursæ mucosæ (Fig. 93, *b*).

Hyaline degeneration of connective tissue possesses no specific staining reactions, as does amyloid. Staining with Van Gieson's (acid fuchsin and picric acid) gives to hyalin in the great majority of cases an intense fuchsin red; but this reaction is sometimes wanting. It is probable that the degeneration of connective tissue known as hyaline represents a variety of degenerative conditions. By many authors hyaline coagula of exudates, occurring in the tissues, are included in this group.

a

b

Fig. 92.—Hyaline degeneration of the connective tissue of a colloid goitre. (Alcohol, Van Gieson's.) *a*, Follicles containing colloid; *b*, hyaline connective tissue; *c*, blood-vessel. × 300.

In many cases (thickening of the heart-valves or of the intima of arteries) the tissue appears on microscopical examination to be very thick and dense, and from this fact the condition has been designated **sclerosis**. The cause of the thickening and homogenous character is not known. The gradual disappearance of the nuclei, the subsequent calcification (see § 66), or softening even to the point of complete disintegration (for example in sclerotic areas of the intima), the sequestration of the altered tissue from the normal (for example, in the degenerated portions of the walls of the bursæ), all point to the fact that the process is essentially degenerative in character.

In other cases the appearance of the hyaline tissue resembles closely that of amyloid degeneration, and there is associated with the hyali

change a pronounced increase of bulk, particularly so in the case of hyaline degeneration of the small vessels of the central nervous system, glomeruli, and the lymph-glands (Fig. 94, *a*, *b*), more rarely in the hyaline degeneration of the connective tissue itself. There occur, moreover, though very rarely, certain forms of hyaline degeneration involving several organs, the heart (Fig. 95, *b*, *c*), serous membranes, intestinal wall, etc., with the formation of glassy masses, which in part give the amyloid reaction, and in part do not. In proliferations of the conjunctiva there have been frequently observed hyaline degenerations of the reticular ground-substance with nodular thickenings of the same; and these changes give the amyloid reaction only in part. It may therefore be assumed that there is a form of hyaline degeneration of the connective tissue, which is closely related to amyloid, and may become changed into the latter (see § 62); and that it arises through the deposit of a hyaline insoluble albuminous body which is probably derived from the blood.

FIG. 93.—Hyaline degeneration of the connective tissue of the wall of a tuberculous bursa. (Müller's fluid, hæmatoxylin, and eosin.) *a*, Fibrous connective tissue; *b*, hyaline connective tissue. × 40.

FIG. 94. FIG. 95.

FIG. 94.—Hyaline degeneration of the blood-vessels of an atrophic axillary lymph-gland. (Alcohol, carmine.) *a*, Hyaline vessel with open lumen; *b*, obliterated vessel. × 200.

FIG. 95.—Hyaline degeneration of the connective tissue of the myocardium. (Alcohol, hæmatoxylin, carmine.) *a*, Normal connective tissue; *b*, hyaline connective tissue; *c*, hyaline masses; *d*, transverse section of normal muscle-cells, *e*, of atrophic (*e*). × 250.

The preparation shown in Fig. 95 was taken from the heart of a woman of fifty-five years of age, the greater part of the heart-wall presenting a hyaline degeneration In both endo- and pericardium there were numerous hyaline nodules and flattened masses. The muscle tissue was in part degenerated, as shown in the figure. Associated with this condition there was extensive degeneration of the blood-vessels, particularly of the intestines, tongue, lungs, heart, and urinary bladder. The peritoneum was also thickly covered with hyaline nodules. The fact that the small areas and the periphery of the larger ones gave no iodine-reaction, while the central portions of the larger areas did so, appears to point conclusively to a close relationship between hyaline degeneration and amyloid. A similar case has been described by Steinhaus.

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§ 65. **Hyaline products of connective-tissue cells** arise in the first place from spherical masses of *flat connective-tissue cells arranged in concentric layers*, which, in a manner similar to the cornification of epithelial cells, become changed into *a hyaline substance containing no nuclei*. These formations occur most frequently in the meninges, the choroid plexus, and the pineal gland, and in the new-growths arising in these regions. Through subsequent calcification they lead to the formation of laminated concretions of calcium salts (see § 66, Fig. 103).

Another kind of hyaline formation probably owes its origin to a secretory activity of the connective-tissue cells. This may be designated *secretory connective-tissue hyalin*, but it must be noted that under this term there is included a variety of different formations, and that, as in the production of colloid, the *cells as a whole may be converted into hyaline products*.

Further belong here certain granules and spherules of hyaline appearance which stain especially intensely with fuchsin, though staining also with methyl violet, gentian violet, etc.; and which are known as *fuchsinophile bodies*. They are also often called Russel's bodies from the fact that they were described closely by Russel, who regarded them as parasitic fission-fungi.

Fuchsinophile bodies are found both in normal and in slightly altered tissues (adrenals, various mucous membranes—as that of the stomach—in the brain, spleen, and lymphadenoid tissues), also in inflamed tissues (particularly the mucous membranes, for example, of the stomach), inflammatory new-growths (polypi of the stomach), and in connective-tissue tumors. They are partly intracellular, sometimes in great numbers, and partly extracellular. They are to be regarded as cell-products, probably of the nature of a cell-secretion, or formed as the result of the disintegration of the cells. Of their genesis and their composition nothing definitely is known; it is possible that

they have a close relationship with the mast-cells. Those occurring in the brain and spinal cord are generally classed with the corpora amylacea (§ 63), even when they give no specific iodine reaction.

Finally, there should be considered in this connection the larger *hyaline spherules and casts of tubes* (changed blood-vessels) resembling epithelial colloid, which are not infrequently seen in sarcomata (see Endothelioma and Angiosarcoma), inasmuch as these formations are also to be regarded as products either of a secretory or of a degenerative process on the part of cells.

The *significance of the granules* of eosinophile and mast-cells, as well as the neutrophile granules of the leucocytes (which stain with a neutral dye obtained through a mixture of acid fuchsin and basic methyl green), cannot be positively stated at the present time. *Ehrlich, Heidenhain,* and *Löwit* regard the granules of the leucocytes as secretory products of a specific metabolism of the cells in which they are found, so that these cells may be looked upon as unicellular glands. On the other hand, *Weidenreich* regards the eosinophile cells as lymphocytes that have taken up the fragments of disintegrated red blood-cells, their nuclei in this process assuming the polymorphous form.

Arnold regards the cell-granules which may be demonstrated by means of especial stains in leucocytes, pus-corpuscles, bone-marrow cells, and also in other cells, not as granules of secretion, but as representing changed structural elements of the cell arising out of a metamorphosis of the plasmosomes—that is, the microsomes of the cell-cytoplasm (see § 80). Acidophile cells may be transformed into basophile, or the reverse may occur; these phenomena are to be regarded as the expression of different stages of development with changes in the physico-chemical properties. *Hesse* has expressed a similar opinion.

The formations described in §§ 64 and 65 as *connective-tissue hyalin* are undoubtedly pathological products, which differ from each other in so far as their mode of origin and their chemical composition are concerned. Since we do not yet know the nature of the processes leading to these hyaline formations, there is nothing to do but to group them according to definite points of view.

Von Recklinghausen gives to the term *hyalin* a much more comprehensive meaning than I do. He includes under the head of hyaline degeneration different pathological changes which I have placed under other heads. He defines hyalin as an albuminous body which stains intensely with eosin, carmine, picrocarmine, and acid fuchsin; is homogeneous and strongly refractive; is but slightly changed by acids; and in its resistance to alcohol, water, ammonia, and acids resembles amyloid, but does not give the iodine reaction. As hyalin he includes epithelial colloid and the hyaline products of connective tissue cells, as well as hyaline degeneration of the ground substance of the connective tissue, also hyaline thrombi, and the hyaline coagula of inflammatory exudates, and hyaline tissue-necroses. According to this author, all of these formations result from the fusion of the elements of neighboring cells.

From their external appearance, all of these products may be properly designated *hyalin;* but the following varieties must be recognized: *epithelial hyalin* (colloid, keratohyalin), *connective-tissue hyalin* (hyaline degeneration of the ground-substance of connective-tissue, hyaline products of cells, and cells which have become hyaline), *blood-hyalin* (hyaline thrombi), *exudative hyalin* (hyaline coagula of exudates on mucous membranes, serous surfaces, inflamed connective tissue, in the urinary tubules, tubercles, etc.), and *hyaline tissue-necroses.* In the case of connective-tissue hyalin a distinction must be made between the hyalin formed as a secretion in the cells (closely related to epithelial colloid, in its mode of origin), and hyaline degeneration of the ground-substance of connective tissue.

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See also § 64.

XIII. Petrifaction of the Tissues and the Formation of Concretions and Calculi.

§ **66.** It is, on the whole, of rather frequent occurrence for firm crystalline, or amorphous, granular masses to be deposited in various parts of the body-tissues; and when such deposits are of such extent as to cause hardening of the affected tissue, the resulting condition is known as **petrifaction**, or when the deposit consists of lime-salts (particularly phosphates) as **calcification**.

The deposit may occur, in the first place, in a tissue which forms an integral element of an organ, and which bears its normal relation to the surrounding tissues. In other cases it takes place in portions of tissue which have been loosened from their surroundings; or insoluble substances which have become changed into a firm state; or, finally, in foreign bodies which have entered the body from without, and form the centres of a process of incrustation.

In the first case there arise **petrifactions of the tissues**; in the second, **free concretions and calculi.** It is to be noted, however, that under certain conditions free concretions may become firmly attached to the tissues of the organ in which they lie, by means of tissue-proliferations extending into or surrounding them. On the other hand, a calcified portion of tissue may in the course of time gradually become loosened from its surroundings and ultimately form a free concretion.

A **deposit of lime salts** occurs in the form of very fine colorless granules (Fig. 96) which when treated with silver (von Kossa) take on a black color (formation of silver phosphate) (see Figs. 97, *b*, 99, and

100, *B*, *b*). When lying closely crowded together they become confluent, and thus give rise to the formation of chalky foci (Fig. 97, *b*) that are usually not sharply circumscribed, but may form also circumscribed spherical concretions (Fig. 98). In the blood-vessels the calcification may begin either in the connective tissue, muscle-fibres, or in the elastic tissue.

FIG. 98.—Calcification of the media of the aorta. × 350.

The *cause of tissue-petrifaction is to be found chiefly in local tissue-changes*, in that the deposit of lime-salts usually occurs in places where the tissue has already died or is in process of degeneration and necrobiosis. For example, lime salts may be deposited in pulmonary infarcts (Fig. 99), thrombi, in necrotic foci arising during the course of inflammations, also in dead cells, particularly renal epithelium (Fig. 101, *d*, *e*), and liver-cells (von Kossa) that have been killed as the result of intoxications (mercuric chloride, lead, aloin, bismuth, copper salts, iodine, and iodoform). A very frequent antecedent to the deposit of lime-salts is the occurrence of hyaline degeneration of connective tissue, often associated with a deposit of fat. This occurs, for example, in the thickened intima of the blood-vessels and heart-valves, in the media of the medium-sized arteries, particularly in the extremities, in inflammatory new-formations of connective tissue (for example, in the serous membranes), in the connective tissue of the kidney pyramids of old people (Fig. 100, *A*, *B*),

a

b

c

FIG. 97.—Calcification of the media of the femoral artery. (Silver preparation.) *a*, Intima; *b*, media; *c*, adventitia. × 40.

and in degenerated thyroid glands. In dying adipose tissue (fat necrosis in the neighborhood of the pancreas) chalky soap may be formed.

The hyaline character of the degenerated connective tissue shows well both in staining with Van Gieson's and with simple hæmatoxylin. In the case of the latter stain the calcified connective tissue (with the exception of that fully calcified) becomes a diffuse dark blue color (Fig. 100, *A*, *c*). The same staining reaction occurs also in the case of calcified necrotic cells (Fig. 101, *d*, *e*). This reaction holds good only for the deposit of carbonates and phosphates, but not for the oxalates of lime.

In rare cases there may occur a deposit of lime-salts in organs which

show but slight changes—for example, in the lungs. Since in part of such cases there is found at the same time a more rapid absorption of the skeleton (senile atrophy of the bones, destruction of the bones by tumors), this deposit is regarded as metastatic in nature, due to the overloading of the blood with lime-salts. Even under these circumstances the immediate cause of the calcification is local, and is dependent upon

FIG. 98.—Calcified vessels in the cerebellum. (Alcohol, hæmatoxylin.) × 100.

retrogressive changes—in the lung tissue (senile atrophy, obliteration of vessels, venous congestion); and the increased absorption of the skeleton is but a favoring factor. According to investigations of Kockel and Kischensky the elastic lamellæ of the small and medium-sized vessels in particular become calcified, but the elastic fibres and capillaries of the alveolar septa are also involved.

The calcification may affect either small or large areas, and in the latter case causes a hardening and white coloration of the tissues. Occasionally it appears in the form of sharply circumscribed spherical, or

FIG. 99.—Calcification of a necrotic lung in the periphery of a hæmorrhagic infarct six weeks old. (Formalin, silver treatment.) × 100.

nodular (Figs. 102 and 103, *a*, *b*, *c*), or long spicule-like formations (Fig. 103, *d*), or as cactus-like formations, and there arise in consequence **concretions lying within the tissue** that occasionally may be recognized even with the naked eye. Under physiological conditions such concretions are found in the form of laminated chalky spherules in the pineal gland and the choroid plexus, forming here the so-called brain-sand

(acervulus cerebri). As pathological formations they occur in different regions of the outer and inner meninges; in many tumors of the same (psammoma or sand tumors, Fig. 102), also in caseous masses (Fig. 102, *b*) or in indurated connective tissue (Fig. 102, *a*). The origin of these

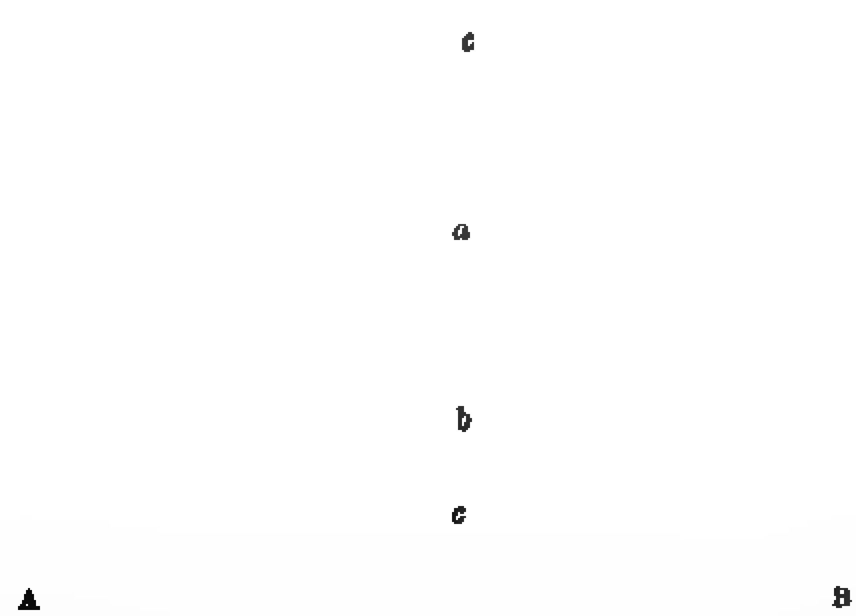

FIG. 100.—Hyaline degeneration and calcification of the connective tissue of the kidney papillæ. *A*, Stained with hæmatoxylin and eosin. *B*, Treated with silver nitrate. *a*, Collecting tubules; *b*, blood-vessel; *c*, connective tissue showing hyaline degeneration and calcification. × 300.

formations may be best studied in the psammomata and is ordinarily to be referred to a transformation of tissue cells (Fig. 103, *a*, *b*, *c*), or of fibrous connective tissue (*d*) into a hyaline mass that may at first still contain nuclei (*a*), and later loses them (*b*, *e*), and then takes up lime-salts. Spherical concretions arise chiefly from hyaline masses formed from cells (*a*, *b*, *c*); and spicules (*d*) arise through the calcification of hyaline connective tissue, but spherical concretions (*e*) may arise also in hyaline connective tissue. The connective tissue which undergoes degeneration and calcification is usually ordinary connective tissue, but calcareous spicules and round concretions may develop also in degenerated vessel-walls.

A true **formation of bone** or **ossification** may follow the calcification of a tissue, either as the result of a new tissue-formation, or of a metaplastic *development of osseous tissue*. This has been observed most frequently in the media of calcified blood-vessels of the extremities, but it may occur also in calcified lymph-glands, in the neighborhood of calcified necrotic areas in the lungs, and in thickened serous membranes, etc.

FIG. 101.—Calcification of the epithelium of the kidney-tubules following sublimate poisoning. (Alcohol, hæmatoxylin.) Patient died seven days after the poisoning. *a*, Normal tubules; *b*, tubule with desquamated epithelium; *c*, tubule with desquamated and necrotic epithelium possessing no nuclei; *d*, *e*, tubule with degenerated and calcified epithelium. × 300.

According to the investigations of *Gierke*, calcifying tissues (fœtal bones, the enamel anlage of the dentine, sand bodies of the choroid plexus, placental calcifications, calcified ganglion-cells) contain more or less iron, and there occur also iron-containing cell-necroses (epithelial casts in sublimate poisoning) which stain like calcified tissue,

FIG. 102.

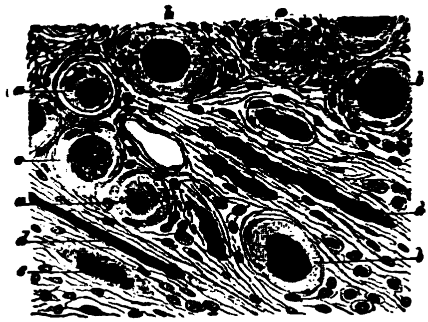

FIG. 103.

FIG. 102.—Calcareous concretions. *a*, Concretions from an inflamed omentum; *b*, calcareous masses from a tuberculous lymph-gland which had undergone caseation. × 200.

FIG. 103.—Section from a psammoma of the dura mater, with concretions. (Alcohol, picric acid, hæmatoxylin, eosin.) *a*, Hyaline nucleated spherule with enclosed calcareous granule; *b*, calcareous concretion with hyaline non-nucleated capsule, embedded in fibrous connective tissue; *c*, calcareous concretion surrounded by hyaline connective tissue; *d*, calcareous spicule in connective tissue; *e*, calcareous spicule containing three separate concretions, embedded in the connective tissue. × 175.

but are not calcified. In other cases (fully developed bone in extrauterine life, calcified thrombi and calcified vessels) iron is not present.

Klotz (*Jour. of Exper. Med.*, 1905, 1906) suggests that the formation of calcium soaps is the first step in the formation of pathological masses of calcification, these soaps later undergoing a transformation into the less soluble phosphate and carbonate.

Wells (*Jour. of Exper. Med.*, 1905) found but minute traces of calcium soaps in calcifying matter. It is, therefore, probable that calcium-soap formation may be an important step in the process of pathological calcification, but is not an essential one. The especial affinity of calcium for cartilage, hyaline connective tissue, etc., cannot at present be explained.

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See also § 68.

§ 67. The more common petrifactions consist of deposits of phosphate of lime, sometimes of carbonate; with these some magnesium salts may be mixed. Under especial conditions there occur also **deposits of uric-acid salts**; particularly in the disease known as **gout**, which is a chronic disturbance of the general nutrition characterized by a *uric-acid diathesis* leading to a deposit of uric acid in the tissues.

FIG. 104.—Deposits of urates in the knee-joint, in a case of gout. *a*, Condyles of the femur; *b*, urate deposits on the cartilage. Two-thirds natural size.

Gout is usually inherited, and but rarely acquired; it occurs most frequently in certain regions, as, for example, in England and in North Germany; and is very rare in other countries, as in South Germany. Of the ultimate cause of the disease we have as yet no positive knowledge. It is characterized chiefly by the deposit in the body of uric-acid salts, chiefly sodium urate, with which small quantities of carbonate and phosphate of lime are sometimes associated (Fig. 104, *b*). The deposit of these salts takes place usually during acute, typical paroxysms characterized by pain and inflammation, but very great departures from a typical course may occur. The deposits are found in the kidneys, skin, subcutaneous tissue, tendon sheaths, tendons, ligaments,

FIG. 105.—Deposits of needle-shaped crystals of sodium urate in the articular cartilage. (After Lancereaux.) × 180.

bursæ, and articular cartilages (Fig. 104), but may finally be present in almost all the organs. The metatarsophalangeal joint of the great toe is a favorite site of deposit, and often the first part affected. The deposits consist essentially of clusters of fine slender needles (Fig. 105), in whose neighborhood the tissues are degenerated or necrotic; and from this it may be assumed that the urates entering the tissues in solution give rise to the necrotic changes in the latter.

The areas of necrosis and incrustation are at first of small size, but occasion inflammation and tissue-proliferations in their neighborhood. Later, with the occurrence of other paroxysms the deposits become larger, so that *large nodules* (the so-called *tophi*) are formed. These consist of white, plaster-like masses, and under certain conditions may form marked nodular thickenings in the joints and tendons (Fig. 106).

In the joints the articular cartilages at first appear as if sprinkled over with plaster-of Paris (Fig. 104, *b*), but later the white masses penetrate deeper and may permeate the entire articular cartilage. In the kidneys the tissue-necrosis caused by the uric acid, and the resulting inflammation may lead to contraction and induration of the organ. The deposit affects chiefly the medullary pyramids, but is found also in the cortex.

FIG. 106.—Gouty nodes of the hand. (After Lancereaux.)

According to Garrod and Ebstein the acute paroxysms in gout depend upon an excessive accumulation of uric acid, either as the result of deficient excretion by the kidneys (Garrod) or of local changes (Ebstein). According to Pfeiffer the gouty predisposition is due essentially to the fact that the uric acid in the body-fluids is produced in a form which is soluble with difficulty, and tends to be deposited in the tissues where it may collect in such quantity as to cause a localized necrosis. The symptoms of the gouty paroxysm are supposed to depend upon an increased alkalinity of the body-fluids caused by especial conditions, as a result of which there follows a partial solution of the deposited uric acid, in the course of which process attacks of pain and symptoms of inflammation are produced. On the other hand, von Noorden regards the formation and deposit of uric acid as a secondary process, due to the local action of a special ferment, and quite inde-

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§ 68. **Free concretions** are formed in the first place in the various ducts and cavities of the body which are lined by epithelium, as in the intestines, in the ducts of the glands pouring their secretions into the intestine, in the gall-bladder, urinary passages, and respiratory tract. In a certain sense the concretions formed in the blood-vessels and serous cavities might also be included in this group, although they are for the greater part firmly united to the surrounding tissues.

Fig. 107.—Faceted stones from the gall-bladder. Natural size.

All free concretions possess an organic base or nucleus. Thus *enteroliths* which form in the intestines have a nucleus of inspissated fæces, or foreign bodies which have been swallowed, such as hairs (*bezoar stones* or *ægagropilæ*), or indigestible portions of vegetable food, etc., in and about which phosphates (ammonium-magnesium phosphate and calcium phosphate), and carbonates are deposited in varying proportions according to the nature of the food ingested. In the mouth-cavity incrustations of the teeth, known as *dental calculi* or *tartar*, are formed by the deposit of lime-salts in masses consisting of mucus, cell-detritus, and bacteria. In the same way there are formed in the *ducts of the salivary glands and pancreas* oval or spherical faceted, or irregularly nodular, glandiform *concretions*, through the calcareous impregnation of a substance derived from the epithelium of the gland.

Bronchial calculi are formed by the calcification of thickened bronchial secretion; the *stones found in veins and arteries* (phleboliths and arterioliths) from the calcification of thrombi; *prostatic calculi* through the calcification of the so-called amyloid concretions; *navel stones* through the retention and incrustation of desquamated epithelium, hairs, and other substances which may enter the navel-depression.

The *biliary calculi* and *gall-stones* found in the bile passages and gall-bladder are in part small granules, and partly larger spherical, oval, or faceted stones (Fig. 107), which on fracture appear to consist purely of crystalline masses. By the employment of proper methods it may be shown that these stones also possess a nitrogenous ground-substance.

FIG. 108.—Section through a small cholesterin stone after removal of the cholesterin. × 13.

According to their essential composition gall-stones may be classed as cholesterin, cholesterin-pigment, bilirubin, biliverdin-calcium, and calcium carbonate stones. The first two varieties are the most common; they present a rayed, crystalline, often laminated fracture; and vary in color and in their mottling according to the amount of bile-pigment present. When no pigment is present they may be colorless and translucent.

FIG. 109.—Uric-acid infarct of the new-born. (Alcohol, hæmatoxylin. Drawn from a preparation that had been washed in water.) Transverse section through the pyramid of the kidney. *a*, Transverse section of unchanged collecting tubule from the papilla; *b*, dilated collecting tubule filled with uric-acid concretions; *c*, remains of concretions after washing with water. × 200.

If the cholesterin be dissolved out of a cholesterin stone by some suitable method, it will be found that the form of the stone is preserved, and a delicate, for the greater part yellowish, mass remains. This, when carefully embedded and cut into sections, is found under the microscope to consist of a delicate, homogeneous substance (Fig. 108) which shows concentric stratification and radiating clefts or spaces which were formerly occupied by the crystalline masses. A similar ground-substance may be demonstrated in other calculi after solution of their calcium salts.

There can, therefore, be no doubt that gall-stones are also the result of the incrustation of an organic substratum, which is in all probability derived from the mucous membrane of the biliary passages and the gall-

bladder. Gall-stones occur especially in advanced years; stagnation of the bile favors their formation. Inflammations of the mucous membranes of the bile-passages (angiocholitis) lead to desquamation and destruction of the epithelium (eventually also to escape of leucocytes), and in the products derived from these pathological changes bilirubin and cholesterin are deposited. When once a concretion is formed it increases in size through the deposit of new products of cell-disintegration which become encrusted with cholesterin, pigment, and calcium. According to Naunyn the originally soft nucleus of the concretion undergoes a change, in that it separates into fluid, and into firm, granular masses of pigment-calcium and crystals of cholesterin which are deposited upon the outer crust, so that the stones may at times contain a cavity filled with the fluid. In the course of time this cavity may again be filled with cholesterin; and also the pigment and calcium in the remaining portions of the stone

FIG. 110. FIG. 111.

FIG. 110.—Coral-shaped stone from the bladder composed of calcium oxalate and phosphate. Natural size.

FIG. 111.—Transverse section of two stones from the bladder, closely fitted together, and consisting of sodium urate and ammonium-magnesium phosphate. Natural size.

may be gradually replaced by cholesterin. Further, calcium carbonate may also be deposited.

The cholesterin masses from which the concretions are formed are derived chiefly from the disintegration of epithelial cells; likewise, the lime-salts combining with bilirubin are also furnished by the mucous membrane.

The *urinary calculi, gravel,* and *stones* are also composed of an organic ground-substance, an albuminous stroma, in which the various constituents of the urine may become deposited. According to location we may distinguish calculi of the kidney and those of the descending urinary passages. In the kidneys the deposits may form only small granules lying in the tissue itself, or in part also free in the lumen of the urinary tubules, in the latter place lying in the products derived from the disintegration of necrotic epithelial cells. This is true in the first place of the calcifications which, as mentioned above, occur in the necrosed renal epithelium after poisoning with corrosive sublimate, bismuth, aloin, copper-salts, iodine, phosphorus, potassium chromate, and oxalic acid. The same thing is true of some of the gouty deposits. Finally, belongs here the so-called *uric-acid infarct of the new-born,* a con-

dition characterized by the appearance of yellowish-red stripes in the medullary pyramids. The condition is not infrequently seen in children dying during the first five weeks after birth. The epithelium of the tubules is usually well preserved, but in places desquamation and disintegration of single cells may be found. The lumina of the tubules are filled with very small, colorless or yellow granules of urates or uric acid, which at times show fine radiating lines (Fig. 109, *b*). On solution of these granules a delicate stroma remains (*c*). If as the result of the presence of the infarct further changes in the epithelium of the tubules are produced, leading to the formation of albuminous material in the tubules, single granules may under certain conditions develop through accretion into large stones, but this occurrence is rare.

In the pelvis of the kidney, ureters, urinary bladder, urethra, and under the prepuce concretions may be formed, either as sand, gravel, or stones. The last-named are oval or spherical, and may be smooth or rough and nodular, not infrequently resembling a mulberry or mass of coral (Figs. 110 and 111). When several stones lie closely together, their surfaces may become faceted (Fig. 111). Those found in the kidney pelvis may form casts of the cavity and of the calyces.

Fig. 112. — Incrusted lead-pencil, 12 cm. long, taken from the male urinary bladder. Reduced $\frac{1}{5}$.

When examined in section, urinary calculi are sometimes homogeneous, at other times distinctly stratified (Fig. 111) or show radiating lines. Not infrequently there may be seen a nucleus and several zones of different appearances. The crystalline masses lie partly in the spaces of the stroma, and partly in the latter itself; and it may, therefore, be assumed that the stroma is a product of the mucosa of the urinary passages, and that its formation follows catarrhal inflammations or toxic necroses of epithelium when these lead to the collection of mucus or cell-detritus in the tubules.

What substances are deposited in a given case in the products of the mucous membrane depends upon the existing conditions. When the conditions favoring stone-formation are associated with a uric-acid diathesis, or if the excretion of uric-acid salts by causing tissue-necrosis has at the same time produced the conditions favoring the development of concretions, the deposits in the organic ground-substance will consist chiefly of urates. Decomposition of the urine with formation of ammonium-magnesium phosphates leads to the production of calculi consisting chiefly of this substance. Cystin calculi may be formed when cystin is excreted by the kidneys, as the result of peculiar metamorphoses of albumin in the intestine, due to the action of bacteria (Baumann, von Udransky, Brieger). When once a stone is formed, the irritation which it causes upon that portion of the mucous membrane with which it comes in contact, as well as the decomposition of the retained urine, favors its further growth by accretion. Likewise, *foreign bodies* (Fig. 112), which have in any way entered the bladder

from without, may *lead to the formation of calculi*, through the irritation which they excite in the mucous membrane of the bladder.

Intestinal calculi are much more common in horses and cattle than in man; since undigested vegetable material and hairs which have been licked off are of frequent occurrence in the intestinal canals of these animals and form the starting-point of such concretions. The true stones, which occur especially in horses, are rather hard masses consisting chiefly of magnesium phosphate; the false stones consist of hairs and vegetable fibres which are more or less encrusted. Occasionally balls are found which consist almost wholly of hair (*ægagropili* or *bezoar stones*). In ruminating animals they are found chiefly in the rumen or reticulum; in hogs, more frequently in the small intestine.

According to *Schuberg*, the enteroliths of herbivorous animals consist chiefly of carbonates; those of carnivorous, of phosphates. The composition of those found in man varies according to the food ingested.

Urinary calculi are classified according to their composition as follows:

1. *Calculi composed chiefly of uric acid or urates.*

Pure *uric-acid* calculi are usually small, yellow, reddish, or brownish in color, and hard.

Stones consisting of urates are rarely pure. They are usually covered on the surface with a coating of calcium oxalate and ammonium-magnesium phosphate.

2. *Calculi composed chiefly of phosphates and carbonates.*

To this class belong stones composed of *calcium phosphate, ammonium-magnesium phosphate*, and *calcium carbonate*. The last two varieties are rare. All these calculi are white or grayish-white. The triple phosphate stones are soft and friable, the others hard.

3. *Stones composed of calcium oxalate.*

These are hard and rough, and of a brown color.

4. *Cystin calculi.*

These are soft, waxy, and of a brownish-yellow color.

5. *Xanthin calculi.*

These are cinnabar-red in color, smooth, and have an earthy fracture.

Ebstein and *Nicolaier* succeeded in experimentally producing urinary calculi by feeding animals with oxamide, an ammonium derivative of oxalic acid. The greenish-yellow concretions thus produced in the urinary passages of dogs and rabbits consisted essentially of oxamide; on section they presented a concentric laminated structure showing radiating striations. They were found likewise to possess an albuminous stroma, which was derived from the necrosis and desquamation of epithelium caused by the action of the oxamide during excretion.

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XIV. The Pathological Formation of Pigment.

§ 69. Both connective and epithelial tissues in various parts of the body contain normally an **autochthonous pigment**, which *lies within the cells*, and consists either of yellow, brown, or black granules, or forms a diffuse yellow or brown coloration of the cells. These autochthonous pigments are known as **melanin, lipochrome,** and **hæmofuscin.** In the epithelial tissues the pigment is found particularly in the lowest layers of the rete Malpighii, which contains pigment in all the pigmented portions of the skin, also in the hairs, in the pigment-epithelium of the retina, and in many ganglion-cells. In the pigment-cells of the skin the granules are chiefly yellow and brown; in the epithelium of the retina they are black. In marked pigmentation of the skin other cells besides those of the rete Malpighii contain pigment. Among the connective-tissue cells, which most frequently contain yellow or brown pigment-granules, are the cells of the choroid, sclera, corium, heart-muscle, muscularis of the intestine, and pia.

FIG. 113.—Large hairy pigmented mole over the back and buttocks, with scattered spots of pigmentation over trunk and shoulders. (After Röhring.)

The **normal autochthonous pigments may be increased** under various physiological and pathological conditions. For example, *during pregnancy the pigment of the skin is usually more or less increased* (*chloasma uterinum*), particularly in brunettes. In *Addison's disease*, a general disease leading to cachexia and which is dependent upon pathological conditions of the adrenals (see § 26), there occurs a decided pigmentation of the skin as a result of an increase of the normal pigment. Not infrequently spots of a bronze color appear in the mucous membranes of the mouth. Further, in atrophic conditions of the heart there is usually an increase of the *normal heart-pigment.* Yellow pigment-granules also

appear in the *voluntary muscles* in conditions of atrophy; and in old persons the *smooth muscle of the intestine* always contains more or less of a yellow granular pigment, so that sometimes the outer surface of the intestine may show a yellow or yellowish-brown coloration.

The most intense grades of pathological pigmentation are met with in *freckles, lentigines, pigmented moles* (Fig. 113) and *pigmented warts*, and in *black melanotic tumors* (see Chapter VIII.). The amount of pigment may be so great as to give the tissues a pure black color.

The pigment lies for the greater part inside of tissue-cells (*chromatophores*), more rarely in the intercellular substance. It is composed of yellow, brown, or black granules; not infrequently individual cells may be diffusely pigmented. In Addison's disease the pigment-granules are found partly in epithelial cells, especially in those lying directly upon the connective tissue (Fig. 114, A, *a*, *b*, and B, *a*), and partly in branched connective-tissue cells (A, *c*, c_1, *d*), from which pigmented processes extend up between the epithelial cells (B, *c*).

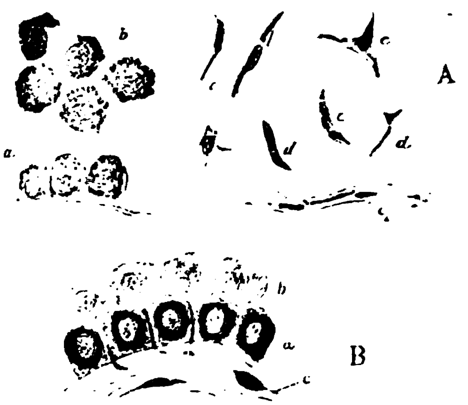

FIG. 114.—*A*, and *B*, Pigmented cells of the skin from a case of Addison's disease with caseous tuberculosis of both adrenals. (Alcohol, carmine.) *a*, Pigmented epithelium cells from the deepest layer, in a section cut at right angles to the surface. *A*, *b*, Pigmented epithelial cells from a section made parallel to the surface. *B*, *b*, Epithelial cells containing no pigment; c, c_1, nucleated pigmented connective-tissue cells, the processes of which, in *B*, push between the epithelial cells; *d*, pigmented cell-processes. × 350.

In the pigmented spots of the skin and in melanotic sarcomata the pigment is partly contained in especially differentiated connective-tissue cells of large size, and partly in apparently normal cells of the given tissue, very often in the connective-tissue cells in the neighborhood of the vessels and in the cells of the vessel-walls.

In the ganglion-cells the pigment is composed of brown granules.

The pigments just described are products of a specific cell-activity; and we must suppose that many connective-tissue cells, ganglion-cells, and muscle-cells are able to form pigment from the material brought to them. In the majority of cases the pigment appears to be formed in the places where it is found; yet different investigations make it probable that the pigment may at times be transported. The pigment of the epidermis and of the hairs, at least in part, is not formed in the epithelial cells themselves, but in branched connective-tissue cells (Fig. 114 A, *c*, *d*, and B, *c*) which lie just beneath the rete, and send processes between the epithelial cells, through which the pigment is transferred to the latter.

The fact that the pigment is often found particularly about the blood-vessels would seem to indicate that the material from which it is formed is derived from the blood, and many authors accept without question the view that the pigment is a derivative of the coloring-matter of the blood. Against this view is the fact that neither in the blood nor in the neighborhood of the blood-vessels are there present evidences of an escape of the red blood-cells or of a disintegration and solution of the same. It

is, therefore, very probable that the pigment is formed either from the circulating albumin or from the albumin of the cells.

The attempt has been made to solve this problem by means of chemical investigations; and the results obtained up to the present time favor the theory that the pigment is a product of cell-activity, and is formed from albuminous bodies. The different forms of **melanin**, in which group the pigments of the skin and choroid are usually placed, are, according to the investigations of von Nencki, Sieber, Abel, Davids, and Schmiedeberg, nitrogenous bodies rich in sulphur, but vary greatly in composition. According to Schmiedeberg these differences depend upon their mode of origin, inasmuch as these pigments represent the *final product of a long series of metamorphoses of albumin;* and in their formation may be compared to the development of humus. The genuine albuminous bodies do not furnish the material for the building up of this final product (Schmiedeberg), but it is derived from sulphur-containing bodies formed by the splitting-up of the albumins, and from which certain carbon-containing groups have already been split off, so that there arise combinations which in proportion to their carbon-content are very rich in sulphur, and from these the melanins are formed.

Iron may be present in small amounts in masses of melanotic pigment, but is usually absent and is not necessary to the production of melanin.

In the case of a very abundant formation, melanin may be excreted in the urine.

Lipochrome is the term applied to the coloring-matter of adipose tissue, corpora lutea, ganglion-cells (Rosin), and of the greenish tumors known as chloromata (Krukenberg). Of the origin and nature of this pigment nothing definite is known.

Hæmofuscin (von Recklinghausen, Goebel) is the iron-free, yellowish granular pigment found in heart-muscle, smooth and striped muscle, in the cells of the glands of the stomach and intestine, in the lachrymal, mucous, and sweat glands, the seminal vesicles, and adrenals. According to von Recklinghausen, this pigment is derived from the blood, but it has not yet been established that it is a hæmoglobin-derivative. The sulphur-content (Rosenfeld) makes it not unlikely that the hæmofuscin granules belong to the melanin group. It is a striking fact that when treated with "fat-stains" the hæmofuscin-granules are found to be fat-containing just as lipochrome stains as fat (Lubarsch).

According to *von Kölliker*, "the pigment of the hair and epidermis is derived from pigmented connective-tissue cells which lie just beneath the deepest layers of the epithelium of the hair-bulbs and of the rete, and send processes between the delicate cells of these layers. These processes divide into long fine ramifications which lie in the intercellular spaces and may even penetrate into the cells themselves, and in this way transfer their pigment to the latter." The pigment of the ganglion cells and of the cells of the retina arises, on the other hand, in the ectodermal cells themselves. *Riehl* and *Ehrmann* agree with *von Kölliker*. *Karg* observed that, following the transplantation of white skin on to the surface of a leg-ulcer in a negro, the white grafted portions became wholly black in from twelve to fourteen weeks: and he concludes that, in the pigmentation of the epidermis, pigmented connective-tissue cells penetrate between the epithelial cells and convey pigment to the latter. Microscopical examination showed the presence of such pigmented processes between the epithelial cells at a time when the latter had not yet become pigmented. *Von Wild* has shown that in melanosarcomata of the skin, pigmented connective-tissue cells may penetrate between the epithelial cells. Similar pigmented connective-tissue cells are found in the pigmented portions of the skin or mucous membranes in cases of Addison's disease, usually, however, in certain areas only and not everywhere.

Histological studies of the mode of formation of the normal pigment in various

animals, chiefly in fishes, amphibia, and reptiles, have led to different conclusions. Thus *Jarisch* is of the opinion that the pigment of the skin and teeth of tadpoles is not derived from the blood, but is a product of the protoplasm, while *List*, on the other hand, believes that the pigment of the skin of fishes and amphibia is formed from hæmoglobin. *Ehrmann* holds that the melanotic pigment of all vertebrates is a hæmoglobin-derivative. According to *Kromayer*, the pigment of the skin of mammals is derived from the protoplasmic fibrillæ of epithelial cells and represents a degeneration-product of the same.

According to *von Fürth*, neither sulphur nor iron is necessary to the formation of melanin. The melanin-molecule contains, however, active atom-groups which enable it to combine with certain complexes rich in sulphur or iron. The investigations of *Bertrand*, *Biedermann*, *Schneider*, *von Fürth*, *Gessard*, and others make it very probable (*von Fürth*) that the formation of melanotic pigment depends upon the action of an oxidative ferment (tyrosinase) upon tyrosin or other hydroxylized substances of an aromatic nature. In the abundant formation of melanin in tumors, melanin or melanogen may be excreted in the urine, so that this at the time of discharge is black or gradually becomes black when exposed to the air and light.

According to *Spiegler*, the results of the chemical investigation exclude the derivation of melanin from hæmatin. He has also demonstrated the existence of a white chromogen which is the cause of color of white sheep's wool and of gray hairs.

In domesticated animals there occurs a peculiar **melanosis of the internal organs,** occasionally associated with melanosis of the subcutaneous tissue. The affected organs (heart, lungs, intestines, etc.) present in varying numbers grayish or black spots, looking like ink-spots, which are produced by the deposit of pigment in connective-tissue cells which otherwise appear normal.

Under the term **ochronosis of cartilage,** *Virchow* described a peculiar iron-free pigmentation of cartilage, in which the different cartilages of the body show a brown or black color. Besides the cartilages, the tendons, capsules of the joints, the periosteum, and intima of the aorta and the heart may show black spots. The pigmentation is dependent in part upon a diffuse imbibition of the tissue and in part upon the deposit of iron-free brownish granules in the cells and ground-substance. The cartilage-tissue shows at the same time retrograde changes, fibrillation, and softening. The pigment probably belongs to the group of *melanins*. During life the urine may have a brown or black color. The condition has nothing to do with alkaptonuria (*Langstein*).

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§ 70. **Hæmatogenous pigments**—that is, *the pigments whose origin from the coloring-matter of the blood may be demonstrated beyond any doubt*—are derived usually from blood which has escaped from the blood-vessels, or has undergone coagulation within the vessels, and are, therefore, *dependent upon local changes*. In other cases they may be caused by a taking-up of blood-pigment into the blood or by a change in the blood itself, whereby granular pigment is either formed in the blood, or hæmoglobin passes into the blood-plasma, so that pigmentation of the tissues results from *metastatic deposits of pigment*. Such pigmentations are known as **hæmachromatoses.**

Both large and small **extravasates of blood** very soon undergo certain changes which are visible to the naked eye. Extravasates in the skin become first brown, then blue, followed by green, and finally yellow. Small hæmorrhages into the tissues, as in the peritoneum, pleura, and lungs, may show for a long time as reddish-brown spots; in decomposing cadavers their color may be slate-colored or black. Large hæmorrhages into the tissue, as in the brain or lungs, assume after a certain time a rust-brown color, which later changes to an ochre-yellow,

yellow, yellowish-brown, or brown pigmentation. All these changes of color correspond to certain changes in the hæmoglobin and in the iron which it contains.

Whenever a **hæmorrhage** occurs in the tissues or into a body-cavity, a certain portion of the blood-plasma and of the *red blood-cells* may be taken up *unchanged* through the lymph-vessels. Another portion of the corpuscles gradually loses its hæmoglobin, the pale stroma of the corpuscles remaining. The *escaped hæmoglobin diffuses* through the surrounding tissues, and from it there are formed the different products which give rise to the changes of color in the neighborhood of the extravasate. A part of the absorbed hæmoglobin may be excreted as *urobilin* (*urobilinuria*); another part, on the other hand, may be precipitated in the tissues in the form of granules or crystals. The latter are *yellowish-red or ruby-red rhombic plates and needles of hæmatoidin* (Fig. 115 B); and represent a frequent residuum of hæmorrhages. A portion of the diffused hæmoglobin may also be taken up by cells, the latter thereby acquiring in part a diffuse yellowish pigmentation, or in part showing the presence of yellow and brown pigment-granules.

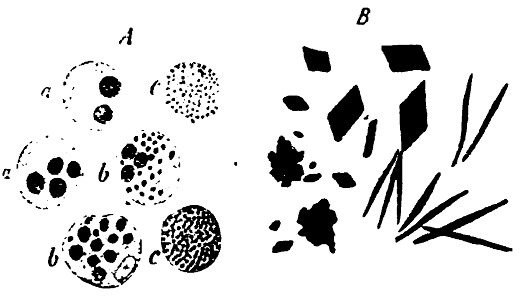

FIG. 115.—*A*, Cells containing amorphous blood-pigment: *a*, those with few large fragments of red blood-cells; *b*, *c*, those containing great numbers of small disintegration-products of red blood-cells; *B*, rhombic plates and needles of hæmatoidin. × 500.

A third portion of the blood-corpuscles disintegrates at the site of the extravasation, and forms *yellow and brown granules and lumps.* The pigment-granules and lumps which arise either directly from the disintegration of red blood-corpuscles, as well as the crystals and granules precipitated from the dissolved hæmoglobin, are often taken up by cells, partly leucocytes and partly cells derived from proliferating tissue; and these form the so-called *blood-corpuscle cells* and *pigment-containing cells* (Figs. 115, A, and 116, *a*, *b*).

At the beginning of the disintegration of the red corpuscles the coloring-matter present is hæmoglobin, but this quickly undergoes changes; and the yellow and rusty masses and granules which are found both in the cells and lying free, and which become changed in the course of time into darker pigment, are no longer hæmoglobin itself, but represent different **derivatives of hæmoglobin.** According to their chemical composition these derivatives may be divided into two groups, one iron-free, the other containing iron. The former is known as *hæmatoidin*, the latter as *hæmosiderin* (Neumann).

Hæmatoidin (*identical with bilirubin*) is a ruby-red (Fig. 115, B) or reddish-yellow (Fig. 116, *b*) pigment occurring either in crystalline form, or as granules, which may be amorphous, but often show a somewhat angular shape (Fig. 116, *b*), suggesting rudimentary and imperfect crystals. Hæmatoidin is soluble in chloroform, carbon disulphide, and absolute ether; and insoluble in water and alcohol. It would appear to be formed especially when hæmoglobin is but slightly exposed to the action of living cells, as is especially the case in the centre of large extravasates and in hæmorrhages into the body-cavities, as, for example,

into the pelvis of the kidney or the subdural space. It may be produced artificially by the introduction of glass capsules containing blood beneath the skin or into the peritoneal cavity in such a way that the blood within the capsules may be exposed to the action of the tissue-fluids but not of the cells.

The granules and crystals of hæmatoidin are found in the tissues either free (Fig. 115, B), or enclosed in cells (Fig. 116, *b*). In the latter case the granules and crystals are usually taken up by phagocytes after they have been formed; though occasionally it may happen that the hæmatoidin while in solution is taken up by fixed connective-tissue cells, for example, cartilage or fat-cells, and then precipitated in solid form.

Hæmosiderin, the derivative of the red blood-cells which contains *iron* in demonstrable quantity microscopically, is usually found in the tissues as yellow, orange, and brown granules and lumps which become darker in the course of time. They are for the greater part contained within cells, and in part are formed within the cells.

When treated with potassium ferrocyanide and dilute hydrochloric acid hæmosiderin becomes deep-blue through the formation of Berlin blue (ferric oxide salt of hydroferrocyanic acid) (Fig. 116, *a*). When treated with ammonium sulphide there is formed a black sulphide of iron.

Hæmosiderin appears to be formed particularly (Neumann) when the blood in an extravasate or in a thrombus is subjected to the action of cells; and it is consequently seen more frequently in small extravasates and at the periphery of larger ones. The formation of hæmosiderin may take place either within the cells or free in the tissue. The pigment enclosed within cells (sideroferous cells) may have been formed from the

FIG. 116.—Cells containing hæmosiderin and hæmatoidin from an old hæmorrhagic focus in the brain. (Alcohol, Berlin-blue reaction.) *a*. Cells containing hæmosiderin; *b*, cells containing hæmatoidin; *c*, fat-granule cells which have become clear; *d*, newly formed connective tissue. × 300.

remains of disintegrated red blood-cells which have been taken up by the cells, or from dissolved hæmoglobin which has been absorbed by the cells. In favor of the latter mode of formation is the diffuse yellow color seen in both wandering and fixed cells, which becomes blue when the Berlin-blue reaction is applied. Further, when hæmoglobin is excreted through the kidneys, iron-containing pigment-granules form in the renal epithelium; and moreover fixed cells, as cartilage-cells, for example,

which could hardly be supposed to act as phagocytes and take up fragments of red cells, often contain granules of hæmosiderin, even when lying outside of the immediate neighborhood of the extravasate.

The free pigment and the pigmented cells cause a distinct pigmentation of the extravasate and its immediate neighborhood. The pigmented cells soon pass into the lymph-vessels and a *metastasis of the pigment* takes place, as a result of which the pigment is found in the lymph-vessels and their neighborhood, and in the lymph-glands where it is found first in the free cells of the lymph-sinus (Fig. 117). Later it may be taken up by the fixed tissue-cells. In the course of time the hæmosiderin is destroyed and disappears. The view which is held by many, that hæmosiderin is changed into a black melanin, is not supported by the actual facts. The brownish-black granules in the lungs, which have been explained as due to such a change, are found through high magnification (Neumann) to consist of one or several minute particles of carbon surrounded by a coating of hæmosiderin.

FIG. 117.—Accumulation of pigment-containing cells in the lymph-glands after resorption of an extravasate of blood. (Müller's fluid, carmine.) *a*, Cortical node; *b*, lymph-sinus; *c*, cells containing pigment-granules. × 100.

If hæmosiderin is brought into contact with hydrogen sulphide it becomes black; and as the result of such reaction there may be produced in the cadaver black and green spots or a more diffuse discoloration, which are known as **pseudomelanosis.** It is observed most often in the intestine, peritoneum, and in suppurating wounds, since in these regions hydrogen sulphide is more likely to be formed in the course of putrefaction.

Arnold has recently declared that, both in hæmatogenous and exogenous siderosis (see § 71), the *iron-granules* of the *sideroferous* cells (leucocytes, connective-tissue cells, liver-cells, etc.) are not iron-granules which have been taken up from without through phagocytosis, or which have been precipitated within the cells, but are changed cell-plasmosomes which have taken up the iron, converted it, and combined it with themselves. The statements made in the main text (§§ 70 and 71) as to the genesis of a portion of the sideroferous cells harmonize with Arnold's view, but it must be affirmed that a formation of sideroferous cells through phagocytosis also occurs, both in case of extravasates and hæmachromatoses due to intravascular destruction of the red blood-cells.

Pseudomelanosis is not produced, as many authors believe, by the action of hydrogen sulphide upon the blood, but is formed by the action of hydrogen sulphide upon hæmosiderin. According to the investigations of *Zeller*, *Arnold*, and *Ernst*, black pigment may also be formed during life, through the action of bacteria which produce hydrogen sulphide. Pseudomelanosis of the human hæmolymph-nodes (*Warthin*) may occur in colon-bacillus infections as the result of the action of H_2S in the blood upon the hæmosiderin deposited in the glands following an excessive hæmolysis.

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§ 71. **When large numbers of red blood-cells break down in the circulating blood,** a portion of the dissolved hæmoglobin or methæmoglobin may pass into the plasma, or, on the other hand, fragments of red cells may be carried about in the circulation. Such a destruction of red cells occurs to a marked degree in poisoning with arsenic, toluylendiamin, potassium chlorate, and morels; to a lesser degree in other diseases, such as many infections, malaria, pernicious anæmia, and in overheating of the body. The passage of hæmoglobin or methæmoglobin into the blood-plasma leads to the condition of *hæmoglobinæmia,* in which the blood-plasma is colored red. When the amount of dissolved hæmoglobin in the blood is large, a portion may be excreted through the kidneys, giving rise to *hæmoglobinuria* or *methæmoglobinuria,* in which conditions the urine may present a bloody appearance, or a color varying from a clear brownish-red to a dark reddish-black. This occurs particularly in the case of the first-named poisons, but also occasionally after the action of other injurious influences, as, for example, after exposure to cold (periodical hæmoglobinuria).

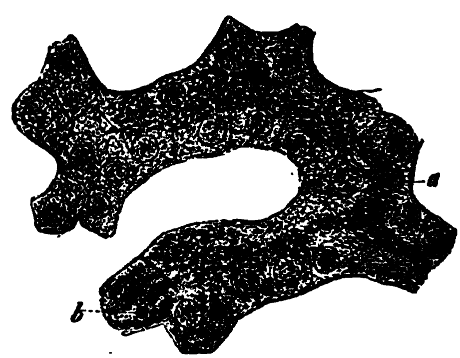

FIG. 118.—Infiltration of the cells of the liver-rods with yellow hæmosiderin granules, from a case of pernicious anæmia. (Osmic acid.) *a*, Hæmosiderin; *b*, cells in a state of fatty degeneration. × 250.

When *formed products* arise from the disintegration of the red cells, as, for example, after extensive burns, they collect first in the

capillaries of the liver, spleen, lymph-glands, and bone-marrow, and to a less extent in other organs; and are sooner or later taken up by cells.

As the result of an increased supply of hæmoglobin to the liver the functional activity of this organ is increased, so that the *amount of bile-pigment in the bile may be much greater than normal;* and under certain conditions oxyhæmoglobin may appear in the bile (Stern). When the blood-destruction is very great, the liver may not be able to dispose of

FIG. 119.—Hæmochromatosis of the liver. (Alcohol, carmine.) *a*, Acini; *b*, peritoneum; *c*, branches of the portal vein; *d*, infiltrated periportal connective tissue; *e*, pigment lying within the liver-acini; *f*, central veins. × 20.

all the blood-pigment brought to it; and in consequence **derivatives of hæmoglobin are deposited**, partly in the liver and partly in other organs, or may be in part **excreted by the kidneys.** In this way there may arise a more or less extensive **hæmochromatosis** of different organs, the cells of which show an ochre-yellow or brown color.

The derivatives of hæmoglobin deposited in this way are partly *iron-free pigments* and partly *hæmosiderin;* but the latter is particularly a frequent cause of pigmentation of tissues, and it is, therefore, proper to speak of **a pigmentation by hæmatogenous siderosis.**

These **deposits of iron-containing pigment** are chiefly in the liver, where they appear partly in the form of yellow granules and lumps, which are for the greater part enclosed in leucocytes lying within the liver-capillaries. Further, they are found also in the form of fine yellow granules, which give the iron-reaction, in the endothelial cells of the capillaries (to which the stellate cells of Kupffer belong), and in the liver-cells (Fig. 118, *a*). In many diseases, as, for example, pernicious malaria or pernicious anæmia, the majority of the liver-cells contain such pigment, so that the liver through the presence of so much iron takes on a characteristic yellowish-brown color.

When large quantities of the products of the disintegration of red

blood-cells are brought to the liver, they accumulate particularly in the periportal connective tissue and in the periphery of the acini (Fig. 119, *d*, *e*). The lumps or granules of iron-containing pigment lie either free in the capillaries, or in the tissue; or are enclosed within leucocytes, liver-cells, connective-tissue cells, or the capillary endothelial cells. The infiltrated area presents to the naked eye a reddish-brown, rusty color.

The iron-pigment which is carried to the *spleen* is deposited chiefly in the pulp within free cells; but granules are also found in the fixed cells. In the *lymph-glands* the iron granules are found chiefly in the free cells of the lymph-channels. In the *bone-marrow* retained hæmosiderin (Fig. 120) is found partly in free cells lying within the capillaries, and partly in the endothelium, also partly in the marrow-cells; the number of iron-containing cells may be very marked.

In the *kidneys* the hæmosiderin granules are most abundant in the epithelium of the convoluted tubules (Fig. 121, *a*), but they are also found in the lumina of the urinary tubules (*b*), in the epithelium of Bowman's capsule (*c*), and in the endothelium of the capillaries. If small particles of hæmosiderin are present in the circulating blood, they will usually be found in the kidney-vessels. When hæmoglobin is excreted by the kidney, drops of this substance will be seen lying in the tubules. In cases of marked deposit of pigment the kidney may show a distinct pigmentation even to the naked eye.

The hæmosiderin, which is found in the different tissues, has been brought to them in the form of small lumps or granules, and is contained chiefly in leucocytes. On the other hand, another part of the iron-gran-

FIG. 120.—Hæmosiderin deposit in the bone-marrow (mixed fatty and lymphoid marrow), in icteru[s]. (Alcohol, carmine, Berlin-blue reaction.) × 300.

ules is precipitated in solid form within the cells from substances brought to them in solution. Since the cells (liver-cells, kidney epithelium, endothelium of the blood-vessels, and the cells of the lymph-glands, bone-marrow, and spleen) not infrequently show a diffuse blue color after the iron-test has been applied, the iron must be diffused throughout the cell protoplasm, and is probably converted later into the granular form. It is also possible that the diffuse coloration may arise in part from a solu-

tion of iron within the cells. According to the observations of different authors it is assumed that besides the colored deposits of pigment, colorless granules of an iron-albuminate may be present in the cells. This theory is supported by the observation that more pigment granules are visible after the iron reaction has been applied, than could be seen before.

The **deposit of iron-free pigments,** *hæmatoidin* or *bilirubin* is not of frequent occurrence in hæmochromatosis, but occasionally yellow granules which do not give the iron reaction are found in the organs named above; and it may, therefore, be assumed that the pigment in part may be constantly free from iron.

By the majority of authors (see *Geyer, loc. cit.*), the *mottled pigmentation of the skin* which develops in *chronic arsenic poisoning*, and which is due to the deposit of small yellowish brown pigment granules in the corium and epidermis (similar to the pigmentation of Addison's disease), is to be classed with the hæmochromatoses. It is to be referred to the degenerative influence of arsenic upon the bone-marrow and the

FIG. 121.—Hæmatogenous deposits of iron in the kidney in pernicious malaria (contracted in Bagamoyo). (Alcohol, carmine, Berlin-blue reaction.) *a*, Convoluted tubules, whose epithelial cells contain iron granules and are stained diffusely blue; *b*, iron-granules in the lumen of the tubules; *c*, straight tubules; *d*, glomerulus; *e*, epithelium of the capsule, containing iron-granules. × 130.

blood. It should be noted, however, that the pigment does not give the iron reaction, and that, according to other observations, pigment in epithelium which is derived from hæmoglobin is not permanent, and that no increased destruction of the red blood-cells occurs in the affected individuals (*Muir*).

The organism supplies its need for iron through the **assimilation of the iron compounds** found in the iron containing articles of food. The iron contained in the iron preparations used for medicinal purposes is absorbed from the small intestine, in particular from the duodenum. Iron absorbed in excess is in part stored up as hæmosiderin in the spleen, bone-marrow, and lymph-glands, or temporarily in the liver; and in part excreted through the kidneys, liver, and large intestine.

In **malaria** *two pigments* are formed as a result of the destruction of the red cells by the malarial parasite. One of these is formed by the malarial plasmodium itself, is contained within the parasite, is black, and gives no iron reaction. Its nature is not known.

The second pigment is hæmosiderin, which passes into the blood-plasma as the result of the destruction of the red blood-cells, and is deposited in the liver, spleen, and bone-marrow. In cases of marked destruction of the blood there may occur also a siderosis of the kidneys (Fig. 121), and an excretion of iron in the urine.

The *green color which is observed in the neighborhood of blood-containing vessels in decomposing cadavers* is to be referred to a formation of sulphur-methæmoglobin through

the action of H_2S on oxyhæmoglobin (*Hoppe-Seyler, Harnack*). In the absence of oxygen, sulphur-hæmoglobin is formed, which possesses a dark-red color (*Harnack*).

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(*Hæmochromatosis; Iron Absorption; Deposit and Excretion.*)

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§ 72. **Icterus** or **jaundice** is a pathological pigmentation of the tissues due to the presence of bile-pigment. Icterus is a symptom which occurs in the course of numerous diseases of the liver, and is of frequent occurrence even in the first days of life (*icterus neonatorum*).

The pathological pigmentation which characterizes icterus is apparent during life, particularly in the skin, conjunctiva, and in the urine; in the cadaver the internal organs—the serous membranes, lungs, kidneys, liver, the subcutaneous and intermuscular tissues, the blood-plasma, clots lying in the vessels, etc.—may show an icteric coloration. In recent cases the icteric color is yellow; in long-standing cases the skin takes on an olive-green or dirty grayish-green color, while similar color-

FIG. 122.—Obstructive icterus of the liver, due to compression of the ductus choledochus by a cancer of the gall-bladder. (Sublimate, alum-carmine.) *a*, Intra-acinous bile-capillaries, moderately dilated and filled with bile; *b*, widely dilated intra-acinous bile-capillary, containing large mass of pigment; *c*, bile-pigment in the liver-cells *d*, d_1, endothelium stained with bile-pigment; *e*, desquamated endothelium stained with bile-pigment; *f*, pigment mass surrounded by cells; *g*, rupture of the pigment contained in a bile-capillary into a blood-capillary, with bile-stained cells in the neighborhood. × 365.

ations occur in the internal organs, particularly in the liver, and occasionally in the kidneys.

Icterus results from the entrance of bile—that is, of bile-pigment (*bilirubin*) *into the blood and fluids of the body.* During such a condition the urine excreted contains elements of the bile, particularly the bile-pigments.

Icterus is a hepatogenous disease, inasmuch as the bile-pigments have their source in the liver. As the result of disease processes in the biliary passages or in the liver itself the normal outflow of the bile is hindered, and the bile is then taken up into the lymphatics and blood-vessels of the liver. Such a damming back of the bile may be caused, for example, by a narrowing or closure of the large bile-ducts through the formation of scar-tissue, through gall-stones wedged in the lumen, or through tumors developing in the bile-ducts themselves, or arising outside of the ducts and compressing them; or through inflammatory processes, abscesses, connective-tissue growths, or tumors of the liver which compress or pull upon, or completely obliterate the smaller bile-ducts, and in this way hinder the outflow of blood from the smaller bile-ducts and capillaries.

In the case of a stasis of bile within the liver-lobules the intercellular bile-capillaries first become dilated and may become filled with large bile-thrombi (Fig. 122, *a*, *b*). The dilatation affects also the blind side branches extending toward the capillaries, and these finally may be broken through, leading to a separation of the liver-cells (Fig. 122, *g*), also to cell necrosis, so that the bile eventually gains entrance into the perivascular lymph-channels and thence also directly into the blood. Further, the bile-pigment is heaped up in granules within the liver-cells themselves (*c*), and the endothelium of the blood-capillaries (d, d_1, e) also becomes stained with bile.

Since there occurs in the liver-cells a double secretion, an external one through the bile-ducts of bile-acids and bile-pigment, and an internal one into the blood-vessels of sugar and urea, it appears reasonable that a passage of bile into the blood may occur not only through stasis of the bile, but also as the result of pathological conditions of the liver-cells due to *infections* and *intoxications*. We may therefore distinguish, in addition to *icterus due to bile stasis* or *stasis parapedesis* (Minkowski), other forms of *icterus due to toxic and infectious parapedesis of the bile* (*paracholia*, Pick); and there are probably many forms of icterus formerly referred to as catarrh of the bile-passages that may be explained in this way.

It is also possible that disturbances of innervation and of the circulation of the liver may be sufficient to bring about an escape of bile into the intra-acinous lymph-channels or into the blood, so that a *nervous paracholia* may also be distinguished.

When bile-pigment, either in solution or in the form of granules and lumps, obtains entrance to the blood, the *tissues of the body become gradually permeated with bile-stained lymph*, and thereby acquire an icteric color. If phagocytes containing granules or lumps of bilirubin are present in the circulating blood, they may accumulate here and there, particularly in the spleen and the bone-marrow. After a time the bile-pigment held in solution within the tissue-lymph may become precipitated as *solid particles of bile-pigment*, chiefly in a granular form, but rarely in a crystalline (the latter form occurs almost entirely in the new-born, in which the crystals are found in the fixed and wandering cells of the connective tissue, in the liver-cells, and in the renal epithelium). The crystals are in the form of rhombic plates and needles, similar to those of hæmatoidin (Fig. 115). In severe cases of icterus very many of the tissue-cells contain pigment, and, as a result of the metastasis of cells containing pigment, accumulations of the latter in the lymph-glands may occur.

In the kidneys in which bile-pigment is being excreted there likewise

occurs an excretory pigmentation, particularly of the epithelium of the urinary tubules (Fig. 123, *a*, *d*), which in consequence may become desquamated. If, as the result of the damage done to the secreting cells through the excretion of the bile-pigment, there are formed, as is usually the case, hyaline casts—that is, hyaline coagula in the albumin-containing urine in the tubules—these likewise become colored by the bile-pigment (Fig. 123, *b*, *c*).

Associated with the deposits of bilirubin in icterus there is always a *deposit of hæmosiderin* which may become so abundant, particularly in the bone-marrow (Fig. 120), spleen, and lymph-glands, and occasionally also in the liver, that the pigmentation of the organs named is dependent in part upon iron-pigment.

FIG. 123.—Icterus of the kidney in obstructive jaundice. (Sublimate, carmine.) *a*, Tubular epithelium containing yellowish-brown granules; *b*, large casts stained yellowish-green; *c*, cast containing pigmented cells; *d*, desquamated epithelium containing bile-pigment granules. × 200.

When an *increased destruction of red blood-cells* takes place within the blood-vessels, hæmatoidin or bilirubin, in addition to hæmosiderin, is formed in different parts of the body (see § 71); but the formation of bilirubin outside of the liver is very slight and is not sufficient to cause any extensive icteric coloration of the tissue, so that *a purely hæmatogenous jaundice does not occur*. The liver is the great elaborator of bilirubin, and in cases of increased destruction of the blood-cells the liver-function is increased and there is an increased production and excretion of bile-pigment. An *icterus due to increased destruction of blood-cells* can occur only when at the same time there are present in the liver such changes as cause a *passage of the bile into the blood*.

The question as to whether there is a hæmatogenous as well as a hepatogenous jaundice has long been an object of discussion, and remains unsettled at the present time, in spite of numerous experimental investigations directed toward its solution. Since, as a matter of fact, bilirubin may be formed in the most different kinds of tissue from extravasated blood, the occurrence of a hæmatogenous icterus would *a priori* appear very probable. Experimental investigations as to the results of the destruction of

red cells in the circulating blood, particularly through the action of arsenic, toluylendiamin, and potassium chlorate, have shown that the derivatives of blood-pigment which are formed in the tissues and there retained for a long time are essentially iron-containing pigments (hæmosiderin), while the production of bilirubin is practically confined to the liver, which for the time being secretes an increased amount of richly pigmented bile.

According to the investigations of *Minkowski* and *Naunyn*, the urine of geese and ducks after removal of the liver contains no bile-pigment—a fact which would indicate that the transformation of blood-pigment into bile-pigment is ordinarily confined to the liver. The inhalation of arseniureted hydrogen for a few minutes is sufficient to produce in geese in a very short time an intense polycholia and hæmaturia, the urine containing hæmoglobin in solution, disintegrating red cells and biliverdin. If the liver from such a goose be removed, the biliverdin quickly disappears from the urine, and no trace of bile-pigment can be demonstrated in the blood. It is therefore evident that in arsenic poisoning the formation of the bile-pigment is confined to the liver, in which organ leucocytes enclosing iron-containing fragments of broken-down red cells are found to be present.

In so far as it is possible to judge from the experimental investigations which have been made up to the present time, a pure hæmatogenous jaundice does not appear to occur. The mere fact of the occurrence of jaundice after intoxications, inhalation of ether and chloroform, transfusion of blood, snake-bite, septicæmia, typhoid fever, yellow fever, paroxysmal hæmoglobinuria, etc., cannot be taken as proof of the existence of a hæmatogenous jaundice. There is, indeed, in these conditions an increased destruction of red blood-cells; but bilirubin is essentially a product of the liver, and if jaundice occurs it can be due only to the fact that a portion of the bile-pigment, which is produced in excess, has found its way into the blood.

According to *von Kupffer* and *Pfeiffer*, the bile-capillaries terminate in intracellular secretory vacuoles; from these, according to *Nauwerck*, *Stroebe*, and *Browicz*, delicate intracellular secretory canaliculi are given off, forming a network around the nucleus. According to *Nauwerck*, the internal secretion of the liver also takes place into very delicate intracellular canaliculi. *Schäfer* describes small nutritive canaliculi within the liver-cell communicating with the blood-capillaries. *Arnold* opposes the view that any preformed system of canals exists within the liver cells.

In the icterus occurring so frequently in the new-born (*Schmorl*) there occurs both a diffuse and a scattered yellowish coloration of the brain limited to the neighborhood of the nuclei, while in later life the brain, even after a long-continued icterus, remains free from pigment. With the nuclear icterus there are also found ganglion-cells stained with bile.

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§ 73. **Pigmentation of the tissues through substances introduced into the body from without** occurs when substances possessing a color of their own gain entrance in some manner to the tissues, where they are able to remain for some time without suffering changes. The number of such substances is large, and the manner of entrance varied. The most *common avenues of entrance* are the *lungs, wounds*, and *intestinal tract*. The

FIG. 124.—Deposit of cinnabar in tattooed skin. (Alcohol, alum carmine.) *a*, Epithelium; *b*, corium; *c*, cinnabar. × 80.

most familiar pigmentation through wounds is *tattooing of the skin*, which is frequently practised by individuals of civilized as well as of uncivilized nations.

The method of tattooing colored figures, etc., consists in the introduction of insoluble granular pigments, such as carbon, india-ink, cinnabar, sepia, burnt sienna, ultramarine, chromate of lead, etc., into slight wounds of the skin. The pigments are rubbed into the wounds, whence they penetrate and infiltrate the tissue in their immediate neighborhood. A portion of the pigment remains in the *corium* (Fig. 124, *c*);

another portion is carried to the lymph-glands, which thereby become pigmented.

The lungs and their lymph-glands may become intensely pigmented through the inhalation of *colored dust*, such as coal-dust, soot, iron-dust, etc. Through the inhalation of coal-dust the lungs may become wholly black.

When coal-dust is taken into the lungs in the respired air a portion of the pigment is carried to the peribronchial lymph-glands, which in consequence may become black. When the deposit is very abundant the lymph-glands may undergo softening and give off the pigment into the lymph-stream. If the glands are situated in the neighborhood of a vein, the pigment-deposit and the softening may involve the vein-wall, so that finally particles of coal-dust may pass into the blood-stream, and be carried to other organs, the spleen, liver, and bone-marrow (see § 21).

FIG. 125.—Deposits of silver in the pyramidal portion of a rabbit's kidney, after seven months' administration of silver salts (experiment by von Kahlden.) (Alcohol, hæmatoxylin.) *a*, Epithelium of the collecting tubes; *b*, connective tissue with brown silver granules. × 500.

From the *intestine* only soluble substances are absorbed, and a permanent pigmentation can therefore occur, only when these are precipitated in the tissue in a solid form, which is at the same time either black or possessing some color. The most frequent of such pigmentations is that known as *argyria*, which is due to the long-continued use of silver-preparations. In this condition the skin may show an intense grayish-brown discoloration, and the internal organs may also present more or less pigmentation. The silver is deposited in the ground-substance of the tissues in the form of fine granules, more especially in the glomeruli, and the connective tissue of the medullary pyramids (Fig. 125, *b*), the intima of the great vessels, adventitia of the smaller ones, in the neighborhood of the mucous glands, the papillæ of the skin, connective tissue of the intestinal villi, and in the choroid plexus of the lateral ventricles. Deposits may occur also in the serous membranes, but the epithelial tissues, the brain, and the cerebral vessels escape. Extensive deposits of silver pigment in the medullary portion of the kidneys may lead to the formation of hyaline connective tissue, which may undergo calcification.

Under especial conditions *iron*, when taken into the body in excessive amounts, may be deposited in the bone-marrow, spleen, and lymph-glands; but the pigmentation thus produced is only rarely visible to the naked eye. In *lead-poisoning* there may be seen a grayish-black discoloration of the gums, which is due to the deposit of granules of sulphide of lead in the connective tissue of the mucous membrane. They are produced through the action of hydrogen sulphide upon the lead, which is present in solution in the mucous membrane.

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XV. The Pathological Absence of Pigment.

§ 74. The **absence of pigment** occurs, in the first place, as a congenital condition, and is then termed **albinism** or **leucopathia congenita.** In a part of such cases the absence of pigment extends over the entire body (*albinismus universalis, Kakerlaken, albinos*); in other cases it is restricted to certain portions of the skin (*albinismus partialis*). In those parts of the skin which are destitute of pigment the hairs likewise may contain no pigment, and appear white or yellowish-white (*poliosis* or *leucotrichia congenita universalis, et circumscripta*). In universal albinism the pigment of the retina, choroid, and iris may also be wanting, so that consequently the choroid, from the amount of blood which it contains, appears red, and the iris, according to the angle of observation and the degree of illumination, will appear either bluish-white or red. On microscopical examination no pigmented cells can be found.

FIG. 126.—Vitiligo endemica (after a photograph received from Professor Münch.)

A second form of absence of pigment is that condition which is known as **vitiligo** or **leucopathia acquisita.** This occurs later in life, either as a sequela to certain well-known diseases (scarlet fever, typhus, recurrent fever), or as a symptom of an epidemic disease of unknown etiology (vitiligo endemica), or finally without any recognizable cause. The formation of white spots, within which the hairs are also white (*leucotrichia acquisita circumscripta*), takes place usually symmetrically, and may extend over the greater part of the body (Fig. 126). The white

areas are surrounded by a border of more deeply pigmented skin; and this suggests that with the disappearance of the pigment at one point the pigment is transferred to adjacent parts. The loss of color in the hairs (even as in old age) begins always in the root, no more pigment being transferred from the hair-papilla to the hair-bulb. Finally the pigment-cells of the papilla disappear altogether.

A third form of loss of pigment is associated with traumatic or infectious *inflammations* of the skin, particularly in syphilitic exanthemata and in leprosy; this condition is known as **leucoderma.**

In scars of the skin which remain white, the newly formed tissue replacing the defect does not possess the power of producing pigment; and consequently represents a colorless cicatrix covered by epithelium. Not infrequently such a scar may be surrounded by a pigmented border. In mild forms of inflammation, in which the tissue of the skin suffers no loss (syphilis), the disappearance of color may immediately follow the inflammation, or not until later, in which case there may occasionally occur a preceding stage of increased pigmentation. According to Ehrmann the lack of pigment in such cases is to be explained either by the fact that no chromatophores are present in the corium to furnish pigment to the epithelium, or the changed epithelium is not able to take up the pigment from the latter when present. The pigment which still remains in the cutis may then be absorbed.

According to *Münch*, vitiligo is of common occurrence in Turkestan, and is considered by the natives (Sarts) to be contagious, so that they isolate the individuals affected with this disease and confine them with lepers in enclosed courts. It is probable that in the literature vitiligo endemica has been many times mistaken for lepra maculosa, and has been described under the designation "white leprosy of the Jews."

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XVI. The Formation of Cysts.

§ 75. A **cyst** is a circumscribed cavity which is shut off from the surrounding tissues by a connective-tissue membrane or by tissue of a more complex structure, and possessing contents differing in nature from the capsule. Cysts may occur in any tissue. When composed of but a single chamber, the cyst is called a *simple cyst;* when divided into a number of compartments, it is known as a *multilocular cyst.*

The most common form is the so-called **retention-cyst,** *which arises from the accumulation of secretions in preëxisting spaces which are lined with epithelium or endothelium.*

In **glands provided with an open duct,** retention-cysts will be formed as the result of the obstruction of the duct, provided that actively-

secreting epithelium still exists behind the point of obstruction. Such cysts are of frequent occurrence in the sebaceous glands, hair-follicles, uterine glands, mucous glands of the intestinal tract, tubules of the epididymis (Fig. 127, *c*), urinary tubules; less frequent in the biliary passages, in the breast, pancreas (Fig. 128, *b*), in the glands of the mouth, etc. **Larger open canals,** such as the ureters, vermiform appendix, and tubes (Fig. 129, *c*), may also undergo cystic dilatation as the result of the collection of secretions. The obstruction of a given duct may be due to accumulation of secretion, to the formation of adhesions (Fig. 129, *e*), cicatricial obliteration, compression, or constriction of its lumen.

FIG. 127.—Section of the testicle and epididymis, with multiple cysts in the head of the epididymis. *a*, Testis; *b*, epididymis; *c*, multilocular cysts. Slightly reduced.

Closed glandular cavities and tubes, such as the follicles of the thyroid and the glandular tubes of the parovarium, may also become cystic when their walls produce an abnormal amount of secretion. Likewise, the **remains of fetal passages and clefts,** as, for example, remains of the branchial clefts, urachus, Müller's ducts, etc., may also become cystic.

Small cysts, such as those developing in mucous glands, vary in size from a millet seed to that of a pea. Larger cysts, such as occur in the liver and ovaries, may attain the size of a fist and even larger.

The **contents of cysts** depend upon the nature of the tissue in which they are formed. Thus the cysts of the sebaceous glands and hair-follicles (*atheroma*) contain a pultaceous, white, or grayish-white, more rarely brown, mass, which consists essentially of squamous cells, in part showing cornification, and also of fat-globules and cholesterin. The cysts occurring in mucous glands contain a mucous fluid which is either clear, or white and cloudy, as the result of the presence of cellular elements.

FIG. 128.—Pancreas cyst, due to dilatation of branches of Wirsung's duct. *a*, Gland-tissue; *b*, cysts; *c*, transverse section of artery; *d*, longitudinal section of vein. Natural size.

Hæmorrhage into a cyst from the cyst-wall gives a red or brown color to the contents. When great numbers of cells are present in the cyst-contents, this may become converted into a semi-solid fatty mass, which

may undergo calcification. Cysts of the thyroid and kidneys contain colloid masses, or a clear though occasionally cloudy fluid.

Retention-cysts lined with endothelium may develop from blood- and lymph-vessels, lymph-spaces, bursæ, and tendon-sheaths. Here also the content of the cyst is dependent upon its place and mode of origin.

As retention-cysts increase in size the stretching of the cyst-wall would ultimately lead to a defect in the continuity of the wall if no *new formation of tissue* took place. Cyst formation is, therefore, not purely a degenerative process; such a new formation of tissue takes place first in the epithelial or endothelial lining of the cyst, but the connective tissue elements of the wall also increase, so that in spite of the stretching

FIG. 129.—Hydrops of the Fallopian tube, with perisalpingitic and periovarian adhesions. *a*, Uterus; *b*, uterine portion of the tube; *c*, abdominal end of tube, showing cystic dilatation and adhesions with the neighboring parts; *d*, ovarium; *e*, membranous adhesion. Two-thirds natural size.

the wall of the cyst becomes no thinner, and under certain conditions may even increase in thickness. Moreover, **cyst formation is often associated with a pathological formation of new glandular tissue** and in this way constitutes a secondary change in hypertrophic or tumor-like growths. It is, therefore, sometimes impossible to draw a sharp line between the simple cystic dilatations of preëxisting gland-canals and gland-spaces, and those tumors, the **cystomata,** which are characterized by cyst formation (see Cystoma). *Endothelial cysts may also develop out of newly formed lymph-spaces and lymph-vessels.*

A second form of cyst is the **degeneration-cyst,** which arises through the partial disintegration and liquefaction of a tissue. Cysts formed in this manner occur in the brain, hypertrophic thyroids, and in tumors. They may contain a clear or cloudy, or at times hæmorrhagic exudate.

A third form of cysts results from the formation of a **connective tissue capsule** around **foreign bodies,** which have found entrance to the tissues, as, for example, about a bullet; or also about **necrotic areas,** or **hæmorrhagic extravasates.**

A fourth variety of cysts is formed by **parasites** which pass through

a cystic stage in the course of their development in the body, and are likewise surrounded by a *connective-tissue capsule.*

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CHAPTER VI.

Hypertrophy and Regeneration. Results of Tissue-Transplantation. Metaplasia.

I. General Considerations Concerning the Processes Known a Hypertrophy and Regeneration, and the Accompanying Cellula Changes.

§ 76. In a general sense, **hypertrophy** is an *increase in the size of tissue or organ, due either to an increase in the size or in the number of the individual elements,* in such a way that the structure of the hypertrophi tissue is like that of the normal, or at least does not differ essentially from it.

In a more limited sense *hypertrophy is an increase in size due to an enlargement of the individual elements alone; the enlargement due to an increase in the number of the individual elements* being designated as *hyperplasia.*

Hypertrophy may result from morbid impulses inherent in the germinal cells, or from influences acting during the life of the individual.

If an abnormal tissue-increase occurs during the period of embryonal development, or of extra-uterine growth, and if no influences are recognizable that would account for the increased growth, the condition may be explained as the result of a **congenital predisposition,** and may be designated as a **hypertrophy due to a congenital anlage.** If the enlargement affects the entire body, for example, if a newly born chil weighs 5–8 kgm., or if an individual should reach the height of 180–2 cm., the condition is called a **general giant growth.** When the e largement affects only individual parts of the body, as, for example, t entire head or one-half of it, or one extremity, or a finger, or the vulv it is called a **partial giant growth.** The giant growth of several par of one side of the body is designated a *half giant growth;* one involvi

FIG. 130.—Elephantiasis femorum neuromatosa.

all the body-parts is very rare. Hypertrophic growths of the skin and subcutaneous tissues, leading to a disfigurement suggesting the appearance of the skin of the pachydermata, are known as **elephantiasis** (Figs. 130, 131).

In hypertrophic growth of an extremity or of a finger all the elements of the same are uniformly enlarged. In elephantiasis of the extremities the connective tissue of the skin and subcutaneous structures is especially likely to become increased; but the development and structure of these growths vary greatly. In one case all the connective-tissue elements may be uniformly increased, in another case only individual elements; as, for example, the connective tissue of the nerves, blood- or lymph-vessels; or at least, the pathological new-formation takes its start from these. It is therefore possible to distinguish *different forms of elephantiasis* according to the structure of the hypertrophic part: *elephantiasis neuromatosa* (Fig. 130), *angiomatosa*, *lymphangiectatica* (Fig. 131), *lipomatosa*, *fibrosa*, etc.

FIG. 131.—Elephantiasis cruris lymphangiectatica.

If, as a result of some peculiar predisposition of the skin, there occurs a hypertrophy of the horny layer of the epidermis (Fig. 132, *c*), so that the skin becomes covered with horny plates, scales, or even with spines, the condition is designated **ichthyosis**.

FIG. 132.—Ichthyosis congenita. Section through the skin of the trunk of the body (alcohol, picrocarmine.) *a*, Corium, with glands; *b*, papillary body, with rete Malpighii; *c*, hypertrophic horny layer of the epidermis; *d*, dilated hair-follicles, lined with horny epithelium; *e*, hairs. × 40.

This change may be present even at birth (*ichthyosis congenita*); and the new-born child (Fig. 133) may be wholly covered with hard horny plates, which have been split open at different points as the result of the growth of the underlying tissues. The pathological cornification affects chiefly the surface (Fig. 132, *c*), but may extend also into the hair-follicles (Fig. 132, *d*).

In other cases, at a later period of development, as during the first years of life, localized thickenings of the horny layer may develop, consisting of either small scales or plates, or larger ones, giving the skin a rough and checkered appearance. The corium and the papillæ are usually not involved in the ichthyosis; but occasionally the papillary bodies may be hypertrophic and enlarged, thus increasing the rough and nodular appearance of the surface (*ichthyosis hystrix*). When the excessive cornification is sharply limited to areas of small size, there are formed circumscribed warts with rough, epithelial covering, which are known as *ichthyotic warts*. In rare cases there may be developed a more extensive horny layer over the hypertrophic papillæ, whose scales are arranged at right angles to the surface of the skin; and these occasionally may attain to such size that they are called **cutaneous horns** (Figs. 134, 135).

FIG. 133.—Ichthyosis congenita.

The hypertrophic development of hair over those parts of the body where only downy hair, or even no hair at all, should be found is known as **hypertrichosis**. Such an abnormal hairiness may cover a larger or smaller area of the body, and depends either upon a persistence and abnormal development of the lanugo (hypertrichosis lanuginosa fœtalis) (Fig. 136), or upon a pathological development of the secondary hairs. An excessive growth of the nails leads to the condition known as *hyperonychia*, which is often followed by a claw-like deformity of the same designated *onychogryphosis*. It is to be noted, however, that the pathological over-growths of the nails are usually acquired.

FIG. 134.—Cornu cutaneum, from back of hand. (Natural size.)

FIG. 135.—Cornu cutaneum, from arm. (Natural size.)

Next to the enlargements associated with general or partial giantism the **bones** most frequently undergo a form of hypertrophy corresponding to the congenital elephantiasis of the skin. The head is usually affected, the bones of which may undergo a very marked enlargement (Fig. 137), leading to a deformity in which the patient's head comes to resemble that of a lion, hence the name **leontiasis ossea.** Further, there often develop upon the skull or other bones of the body circumscribed bony growths known as **exostoses,** which are inherited and not dependent upon extrinsic influences.

In the **internal organs** hypertrophic processes dependent purely upon intrinsic causes are rare; but the brain, for example, may reach an abnormal size.

It cannot always be definitely stated to what extent hypertrophy of the tissues is to be attributed to a congenital predisposition, inasmuch as many extrinsic influences are able to produce proliferations of tissue similar to those due to

FIG. 136.—Head of a hairy individual, a woman. (After Hebra.)

FIG. 137.—Leontiasis ossea, occurring in a boy affected with general giant-growth. (Observed by Buhl.)

intrinsic causes. For example, cutaneous horns and elephantiasis-like thickenings of the skin may develop as the result of inflammation.

In general, the early appearance of a hypertrophic growth, the hereditary nature of the pathological peculiarity, and the absence of any external etiological factor, speak for the congenital nature of the condition. The fact that later influences may apparently cause the growth does not preclude the existence of a congenital predisposition. Thus the excessive bony growths of the head above mentioned may follow trauma or acute inflammations. External influences may therefore be the exciting cause of the proliferation, but not the primary cause of the same; since we know by experience that the given injurious influences are able to produce such changes only in tissues possessing a special predisposition.

Not infrequently an abnormal tendency to excessive growth may show

itself in a *premature development of certain organs, the structure remaining normal.* The external and internal sexual organs are most frequently affected. Girls, even in the first years of life, may show a development of breasts and external genitals and a growth of hair corresponding to that of the sexually ripe woman; and menstruation may be established at this early period.

The size of the entire body as well as of its separate parts and organs shows considerable variation within physiological limits, according to the race, family, and individual. The variation in the relation of the size of single parts and organs to that of the entire body is less marked.

The average height of the body in well-built individuals is, according to Vierordt ("Daten u. Tabellen für Med.," Jena, 1893), as follows: Men 172 cm., women 160 cm.; of the new-born, males 47.4 cm., females 46.75 cm. The average body-weight in Europe is for men about 65 kgm., that of women about 55 kgm., that of the new-born about 3,250 gm.

The average weight of the internal organs is as follows, the figures in parentheses being for the new-born: Brain 1,397 (385) gm., heart 304 (24) gm., lungs 1,172 (58) gm., liver 1,612 (118) gm., spleen 201 (11.1) gm., right kidney 131, left kidney 150 gm., both kidneys 299 (23.6) gm., testicles 48 (0.8) gm., muscles 29,880 (625) gm., skeleton 11,560 (445) gm. Expressed in percentages of the body-weight the figures for adults and new-born are (the latter in parentheses): Heart 0.52 (0.89), kidneys 0.48 (0.88), lungs 2.01 (2.16), stomach and intestines 2.34 (2.53), spleen 0.346 (0.41), liver 2.77 (4.30), brain 2.37 (14.34), adrenals 0.014 (0.31), thymus 0.0086 (0.54), skeleton 15.35 (16.17), muscles 43.09 (23.4).

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§ 77. The **hypertrophies of the tissues due wholly to extrinsic influences without the aid of a congenital predisposition** owe their origin either to an increase in the activity of the tissue, to diminished use, defective retrograde change, or finally to prolonged or frequently repeated mechanical, chemical, and infectious irritations of the tissues. Under certain conditions the removal of pressure may also give rise to a localized hypertrophy.

Hypertrophy from overwork is most frequently observed in the case of *muscles* and *glands*, but may occur also in other tissues. If the *heart* is called upon to do an extra amount of work as the result of diseased con-

FIG. 138.—Transverse section of a heart showing hypertrophy of the left ventricle, resulting from aortic stenosis and insufficiency. *a*, Left, *b*, the right ventricle. Reduced $\frac{1}{2}$.

ditions of the valves, aorta, or kidneys, and if such conditions exist for some time, that part of the heart-muscle upon which the extra work falls suffers a more or less pronounced hypertrophy (Fig. 138), so that as a result the mass of the heart may reach threefold that of the normal.

In a similar manner the *striated muscles, and the unstriped muscle of the bladder, ureters, uterus, intestine, and blood-vessels* may become hypertrophic as the result of persistent increase in their activity.

As the result of an increase of the supporting strain from whatever cause the *bones* may become thickened, and the bony trabeculæ of the medullary portion become increased in size.

Of the *glands*, the *kidneys*, and *liver* in particular are able to change their size according to the functional demands, and may consequently present a marked hypertrophy. Should one kidney be destroyed the remaining one may become so enlarged that it may reach approximately

the same weight that the two kidneys together originally possessed. Likewise the liver after a destruction of a part of its parenchyma through disease may make good its loss by a hypertrophy of the remaining tissue. Since in this way a compensation for the defect and a restoration of the normal function is brought about, such a tissue-increase may be appropriately designated **compensatory hypertrophy.** The same term may also be applied to muscle-hypertrophy, if through it functional disturbances are compensated. A similar compensatory hypertrophy is said to occur also in the case of adrenal tissue. In the case of other glands, such as the salivary glands, ovaries, testicles, and mammary glands, such a compensatory hypertrophy either does not occur at all, or takes place only during the period of development. The loss of an ovary or testis in adult life can hardly result in an increased activity or hypertrophy of the remaining organ. Extirpation of the larger part of the thyroid gland is not followed by any pronounced hypertrophy of the remaining portion; but, on the other hand, the hypophysis undergoes an enlargement which must be regarded as compensatory. In the case of the *lungs,* an increase in the activity of one portion after the loss of other parts results usually in a permanent overdistention which may lead eventually to atrophy. On the other hand, if during embryonic life a defective development of one lung takes place, the other lung may undergo a compensatory growth, which in the case of total agenesia of one lung may reach a very pronounced degree. For the other organs the general principle may be applied that compensatory hypertrophy is the more perfect the younger the individual. In the case of the brain a compensatory growth of one part after the loss of another is possible only during the early stages of development.

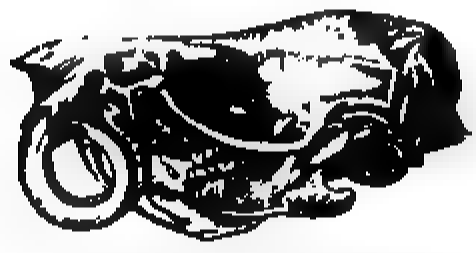

FIG. 139.—Hypertrophy of an incisor tooth of a white rat, the result of an oblique position of the jaw. (Natural size.)

Hypertrophy from lessened use occurs in the case of tissues which are subjected to a constant use. Thus, for example, a diminished desquamation of the horny layer of the epidermis leads to its pathological thickening. If, as the result of the destruction of an opposing tooth or an oblique position of the teeth, the incisor teeth in rodents are not worn down by use, they may grow out into long and curved tusks (Fig. 139). Likewise the finger- and toe-nails may reach an abnormal size either from lack of wear or from being left uncut. **Hypertrophy due to defective retrograde change** occurs in organs which after a definite period of physiological growth undergo a diminution in size. For ex-

FIG. 140.—Elephantiasis scroti in a Samoan nineteen years of age. (After Uhlemann, *Deutsche med. Wochenschr.,* 1895.)

ample, the uterus after pregnancy may remain abnormally large as the result of a failure of involution. The thymus gland, which should begin to atrophy after the tenth year of life, may persist for a much longer period than normally. In bones whose configuration has been brought about under the influence of the surroundings by means of an alternation of building-up and tearing-down, a **lessening of pressure** may be followed by hypertrophy. In idiots whose brains are deficient in size there is very often seen a hyperostosis of the inner surface of the base of the skull (Chiari). A unilateral hyperostosis of the skull is associated with a unilateral hypoplasia of the brain.

Fig. 141.—Acromegaly, according to Erb and Arnold. (Osteo-arthropathy, according to Marie and Souza-Leite.)

Frequently repeated or long-protracted mechanical, thermal, chemical, or **infectious irritations** give rise to proliferative processes leading to tissue-hypertrophies, which according to their etiology and course must be regarded as chronic inflammations; and such new-formations of tissue may therefore be regarded as an **inflammatory tissue-hypertrophy.** They are characterized very often by the fact that, in the enlargement of the organ, not all of its parts are equally involved in the hypertrophy; but certain individual elements, usually the connective tissue, occasionally also the epithelium, undergo hypertrophy to an especial degree, so that the *structure of the organ* (skin, gland, etc.) *is no longer wholly typical.*

If the skin is frequently subjected to mechanical irritation and pressure, as, for example, the toes through an ill-fitting boot, there may arise in consequence thickenings of the horny layer of the epidermis, known as *callus* or *corn* (*clavus*). Prolonged irritation of the skin in the neighborhood of the genital openings, caused by gonorrhœal discharges, may cause a marked elongation and branching of the papillæ with an accompanying thickening of the epithelium, leading to the formation of the warty, cauliflower-like growths known as *venereal warts* or *condylomata acuminata.* Chronic inflammations of the corium and subcutaneous tissue, due to infection or to animal parasites (*Filaria Bancrofti*), not infrequently give rise to extensive fibrous hypertrophies of the tissue known as *elephantiasis* (Fig. 140). Such elephantiasic hypertrophies of the tissue may attain extraordinary proportions. In a similar manner there may occur in the bones, as the result of chronic infectious processes (syphilis,

for example), extensive hypertrophies characterized by an increa formation of bone-substance.

In the majority of cases of those tissue-hypertrophies which app during the course of life as acquired formations caused by external in ences, the *causa efficiens* may be recognized with more or less certain but there are also many cases in which, at the present time, this is eit wholly impossible or possible only to a limited extent. For examp there occur *enlargements of the spleen, and of the lymphadenoid tissue* of lymph-glands and of the lymph-nodes in the mucous membranes, wh are of the nature of hypertrophies, whose causes we are unable to rec nize. Very imperfect, also, is our knowledge concerning the etiology the *enlargements of the distal portions of the extremities* (Fig. 141), rese bling partial giant-growth, which have been described as **acromeg** (Marie), **pachyakria** (von Recklinghausen), and *ostéoarthropathie hyp trophiante* (Marie). In a part of these cases there are an associated largement of the bones of the face and deformities of the spinal colum These changes appear usually in youth or middle age, rarely in old a and show a gradual development.

So far as anatomical investigations have been able to throw lig upon this question, the pathological change consists in an increase of the tissues of the terminal portions of the extremities and of the face, particular of the bony parts, in that the bones become thicker (Fig. 14 and at the same time become the seat of rounded or pointed exostos On the other hand, an increase in the length of the bones has not been demonstrated with certainty in this disease (von Recklinghaus

FIG. 142.—Skeleton of the hand, with hypertrophic bones, from the case of acromegaly pictured in Fig. (After Arnold.)

Arnold). The disease suggests those changes which are seen as the sult of certain intoxications or infections, for example, syphilis, but is not possible at the present time to assign to it any definite cause.

The cause and nature of these pathological phenomena are as yet obscure; and t terms mentioned above are not used by all authors with the same meaning. In G many the designation acromegaly is applied to all forms of enlargement of the ends

the extremities which lead to a paw-shaped deformity of the hands and a gigantesque appearance of the feet, while *Marie*, who first described these conditions, attempts to draw a sharp line between acromegaly and ostéoarthropathie hypertrophiante. He holds that in acromegaly the hands and feet are not deformed, but are symmetrically enlarged, the thickening and broadening diminishing toward the tips of the extremities, so that the terminal phalanges of the fingers and toes are but slightly thickened, while, on the other hand, in ostéoarthropathie hypertrophiante the terminal phalanges are enlarged so as to resemble drumsticks, and the articular ends of the bones are irregularly thickened. In the first affection the lower jaw is lengthened, in the latter it is thickened. *Marie* believes that in many cases ostéoarthropathie hypertrophiante is a sequela of inflammatory affections of the lung- and pleuræ, and designates the condition accordingly as ostéoarthropathie hypertrophiante pneumique, and holds that the connection between these processes is to be found in the taking up into the body-fluids of poisonous products from the inflammatory foci in the lungs, so that the affection of the bones is to be regarded as an infectious toxic hypertrophic inflammation.

By other authors the causes of acromegaly and ostéoarthropathie hypertrophiante are to be sought in a congenital predisposition (*Virchow*), in disturbances of the sexual function (*Freund*), in a diseased condition of the hypophysis (*Henrot, Klebs, Tamburini, von Hänsemann, Benda, Stevens*), in persistence of the thymus (*Erb, Klebs*), or in nervous influences (*von Recklinghausen*); but none of these hypotheses is adequately supported by anatomical and clinical observations. The frequent association of acromegaly with tumors of the hypophysis of different kinds has been definitely determined, but the character of the tumors in some cases would indicate an increase of function, in other cases a diminution or loss of the same. *Cagnetto* is therefore of the opinion that a primary disturbance of metabolism underlies the condition of acromegaly, so that both the bones and the hypophysis are stimulated to hyperplastic proliferation. Although the investigations made up to the present time do not permit a positive conclusion as to the nature of these conditions, they show that they do not represent an excessive growth similar in nature to a partial giant growth, but are *acquired diseased conditions*, which develop either as independent diseases (acromegaly, pachyakria), or as secondary phenomena in the course of other diseases (ostéoarthropathie hypertrophiante pneumique).

The cause of the nodular hypertrophy of the thyroid gland, occurring so frequently in many regions, is wholly unknown.

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§ 78. **Regeneration** is that *process through which tissues which have been destroyed are restored.* Under especial conditions this restoration may

be brought about by an enlargement of existing parts of cells (regeneration of axis-cylinders), but it is *usually the result of new-formation of cells, which arise in all cases through the division of preëxisting cells.*

Regeneration presupposes that the **injured tissue is capable of proliferation**, and is, moreover, a phenomenon which is in all cases dependent upon **extrinsic causes.** In the fully developed organism in which the different tissues and organs have reached their ultimate differentiation, *each tissue can produce only new tissue of its own or a closely related kind.* The **specificity of the tissues** is of so decided a nature that epithelial cells can never give rise to connective tissue, nor can the latter ever produce epithelium. Ectodermal cells cannot produce intestinal epithelium; kidney epithelium can produce only cells having the character of kidney epithelium, but never liver-cells or those of mucous glands, or connective tissue. Muscle-tissue can arise only from muscle-cells. Nerves and neuroglia can never arise from connective tissue. Only cells which are very closely related to each other can arise from the same parent-tissue or pass into each other. Thus the connective tissue of the periosteum can produce either ordinary connective tissue, cartilage, or bone—that is, tissues which are closely related to each other, and which

FIG. 148.—The skin-portion of a laparotomy wound sixteen days old (Müller's fluid, Van Gieson's). *a*, Epithelium, *b*, corium; *c*, subcutaneous adipose tissue; *d*, scar in corium; *e*, new epithelium; *f*, scar in adipose tissue. × 35.

may be regarded as different modifications of the connective-tissue substance.

In *tissue defects in which only single cells are lost* (as, for example, in the loss of single connective-tissue cells), or in the case of a more extensive destruction of cells *without an interruption in the continuity of the connective*

tissue of the blood-vessels (as the loss of localized areas of the surface epithelium, or a group of gland cells or of pulmonary epithelium), a **complete regeneration**, a *restitutio ad integrum*, may take place, and the tissue be restored to a condition corresponding in all respects to that existing before the injury. *After all injuries in which the continuity of the*

FIG. 144.—Healing ulcer of the small intestine, with formation of new gland-tubes in the proliferati[ng] submucosa (Müller's fluid, hæmatoxylin). *a*, Mucosa; *b*, submucosa; *c*, *d*, muscularis; *e*, serosa; *f*, r[e]mains of the floor of the ulcer not yet covered over with epithelium; *g*, overhanging edge of the ulcer; [*h*,] portion of floor of ulcer covered with epithelium; *i*, newly formed glands in the submucosa; *k*, deep cry[pts] lined with epithelium. × 18.

mesodermal supporting tissue is broken, either with or without an associate[d] injury to tissues of ento- and ectodermal origin, the **regeneration** i[s] **incomplete**; in that, at the point of injury there is formed a tissu[e] which departs more or less from the normal structure of the affecte[d] part, and shows a more or less marked loss of functional capacity a[s] compared to the normal tissue. In general this tissue is a new formatio[n] of *connective tissue*, designated as a **scar** (Fig. 143, *d*) or **cicatricial tissue**, in individual organs (as in the heart-muscle) also called a *callosity*, th[e] new connective tissue resembling other formations of connective tissue but not wholly identical with them. In the course of time it come[s] through a gradual change more and more to resemble normal tissue. Defects of the skeleton are replaced by scar-tissue which arises from th[e] periosteum and endosteum, and by virtue of the peculiar properties o[f] these tissues there develops a new-formation of *bone-tissue* within suc[h] scars, the structure coming to resemble closely that of normal bone.

In many cases the *cicatricial tissue* consists purely of *vascularized connective tissue* (Fig. 143, *d*), which later becomes enriched only throug[h] the in-growth of *nerve-fibres* and the gradual development of *elastic fibres*. Scars bordering upon ectodermal or entodermal tissue may become covered by a new formation of epithelium (Fig. 143, *e*). Occasionally th[e] structure of cicatricial tissue may undergo a further development, i[n] that *specific tissue formations* either *grow into it secondarily* or are *preserve[d] in it as remains of preexisting structures*. The first process occurs mos[t] frequently in scars of the mucous membrane of the intestine (Fig. 144) and of glands in the neighborhood of their excretory ducts, and in scar[s] of muscle (Fig. 145). In defects of mucous membranes which ar[e]

placed by scars formed through the proliferation of connective tissue (Fig. 144, *b*, *f*), the surface is first covered with epithelium (*g*, *h*, *k*), later there develop epithelial ingrowths which bear the character of tubular glands (*i*). Gland-ducts (bile-ducts, ducts of the salivary glands) may grow into the developing scar-tissue, and form new tubes or only solid cords of cells. Such a new-formation of gland-ducts may occur not only in the neighborhood of traumatic injuries, but also in the course of hæmatogenous inflammations of the glands in question.

A new-formation of gland-tissue proper in the neighborhood of scars is, on the other hand, wanting in the case of the majority of glands (liver, kidneys, testicles, ovaries, thyroid, mammary glands, and lungs). Only in the case of the salivary glands does the development of the newly formed ducts lead to the formation of gland-lobules.

In muscle-scars (Fig. 145) new muscle-fibres (*d*) grow from the ends of the old ones (*a*), and penetrate into the scar-tissue, so that the scar becomes gradually replaced by muscle.

The preservation of remains of specific tissue-elements in the area of cicatrization may be observed in the case of both muscles and glands, especially in the periphery of traumatic injuries and anemic necroses (Fig. 146), and in most cases also in infectious foci of disease. The preserved gland-remains within the scar usually present an atrophic condition (Fig. 146, *b*), but islands of normal tissue (*d*) may also be enclosed, and there arises the possibility that such may undergo a compensatory growth.

...IG. 145. Scar of muscle and tendon, thirty-two ...s old (Flemming's solution, Van Gieson's). *a*, ... muscle; *b*, tendon; *c*, scar; *d*, newly formed ...scle-fibres. × 100.

In inflammatory processes in glandular organs which are characterized on the one hand by the destruction of the specific parenchyma, and on the other by a new-formation of connective tissue having the character of scar-tissue, there ...e often seen in the diseased area new-formations of scar-tissue con-

taining atrophic remains of the gland-tissue, and between these, island of uninjured gland-tissue in a condition of hypertrophy.

The **mass of the scar** is only rarely equal to the mass of the tiss lost, and there persists after the loss of considerable amount of tissue more or less marked **tissue defect.** Over circumscribed areas of th surface of the skin, mucous membranes, or of glands, the brain, etc such a defect gives rise to a *cicatricial depression.* Numerous cicatrici defects in an organ may occasion an atrophy of the same characteriz by an irregular configuration of the surface.

The loss of the tissues *en masse* of larger portions of the body, as, f example, a toe or a toe-joint, is in man *never again replaced.* Such d fects are only closed in by scar-tissue which on the superficial parts the body becomes covered with surface epithelium.

The **regenerative capacity of tissues** is in man and the mammals slight on t whole. This is dependent upon the fact that the individual tissues show a very hi degree of differentiation, and that also in the event of proliferation they do not lose th differentiation to such an extent as to revert to so embryonal a state that, like the ce of the embryonal anlage, they are able to produce different forms of tissue. In sp of this limitation the regenerative powers of the tissues in general are sufficient restore the continuity of the tissues and to preserve intact the external covering of t

FIG. 146.– Peripheral zone of an embolic scar (Müller's fluid, hæmatoxylin and eosin). *a*, Scar sh ing obliterated glomeruli, but no tubules; *b*, indurated tissue with atrophic tubules, the glomeruli be preserved; *c*, normal cortical tissue; *d*, island of normal tubules in the scar. × 80.

body. If, as the result of a local loss of tissue, the life of the organism be endange through the inability of the local tissues to restore the lost part, there exists in t case of many organs and tissues (liver, kidneys) the power of compensating for such loss through the growth of the remaining normal tissue.

In the lower animals the power of tissue-regeneration is much greater than in t case of the mammals; and further is much greater in the earlier stages of ontogenes so that, in many animals (tritons, ascidians, echinoderms, teleosts), the first two or ev the first four segmentation cells still possess the power of forming an entire embry Insects possess during the larval state a very marked power of regeneration, whi later is lost.

In the case of protozoa each animal may quickly supplement itself through di sion. In the case of the fresh-water polypi small fragments of the body may devel again into the entire animal. The angle-worm is able to replace either its tail or he end when these are cut off. The wood-louse can replace its feet and antennæ, the sn

tentacles and anterior extremity, crabs and crayfish their claws and legs. Salaman-s are able to restore their legs, eyes, and tails, and lizards and slow-worms their s. when these are broken off. In the case of frogs, snakes, and fishes, on the other d. the power of regeneration diminishes as the scale of animal life is ascended, yet does not happen equally in the case of all animals, and animals closely related to h other may show very different capacities for regeneration. Further, in the same mal the regenerative power is not the same in all organs; for example, in tritons the enerative capacity of the internal organs is slight. Moreover, the power to form a portion of the body, as a tail or extremity, for example, does not prove that all tissues of the portion of the body in question possess an especial capacity for pro-ration. In crayfish and crabs the regeneration of the claws and legs takes place only m certain places; in injuries occurring to other points, the new extremity is thrown only at that place where a new-formation is possible. In tritons, fractures of the es heal very slowly, although they are able to reproduce their extremities.

§ 79. The **cause of the cell-proliferation** underlying all hyperplastic l regenerative new-formations of tissue varies according to the condi-ns under which the proliferation occurs. If the new tissue-growth ding to hypertrophy takes its origin from the anlage of the organism ncerned or of a portion of the same, no new stimulus is necessary for appearance; the attainment of the abnormal size is dependent only on the condition that the new-formation of tissue does not lead to ndrances to growth before the full limit of development is reached. hen the proliferation appears first at a later period, something addi-nal is necessary to cause an increase of the normal tissue-formation or start again into activity the cell-proliferation which becomes quiescent the close of the period of growth.

In the case of both hyperplastic and regenerative proliferation the *imulus"* may consist simply in the **removal of hindrances to growth.** perience teaches that the majority of the cells of the body possess the wer in a given case to divide, even those (connective-tissue cells, gland-ls, muscle-cells) in which the processes of cell-division wholly cease long periods of time. This cessation of proliferation may be ex-ained by the assumption that the firm combination of the cells with h other and the formation of the intercellular cement inhibit further iltiplication. It is also possible that chemical and unknown vital luences act in the same manner. Injuries and degenerations of the sues of the most varied kinds can, through the loosening of the cells, d through physical and chemical changes in the intercellular cement bstance and of the tissue-fluids, cause such changes that all hindrances the growth and division of cells are removed.

In addition to the removal of hindrances to growth there may be esent at the same time a **formative stimulus, which increases both e reproductive capacity and the tendency toward reproduction.** rther, such a stimulus may act independently—that is, without the noval of the influences inhibiting growth—and this event is to be sumed in those cases in which after the loss of a portion of an organ e remaining portion (liver, kidney) undergoes a compensatory hyper-phy.

The stimuli which are able to excite growth and cell-division are own only in part. In those cases in which their action may be recog-zed they appear to be *identical with the stimuli which excite or increase nctional and nutritive activity.* In the case of the muscles hypertrophy brought about by increased contraction following nervous excitation. ver and kidney tissue undergo proliferation when, as the result of a s of a large area of gland-tissue, the remaining portions are obliged to

do an increased amount of work—that is, they must out of the circulating blood produce and secrete those substances which, if life is to be preserved, must be given off either externally or within the body.

Whether there exist still other formative stimuli cannot be said with certainty at the present time. An *increased supply of blood and nutrition*, which has been believed by many to act as a formative stimulus, is not in itself sufficient to excite a new-formation of cells and tissue; it gives rise only to an increased deposit of fat. The cells of the body are not fed, they feed themselves; and an increase of nutrition depends upon the activity of the cells. An *increase of the temperature* of the tissues may hasten the process of cell-division and thereby further tissue-proliferation; but it is doubtful if it can directly excite proliferation in a resting-tissue. The local action of heat, which has been observed to be followed by proliferation (for example, in the skin), produces in the first place changes of a degenerative nature, so that the occurrence of proliferation may be also explained as due to the removal of influences inhibiting growth.

Whether there are *chemically active substances* capable of exciting proliferation, besides those present normally in the body, cannot be decided at the present time. The fact that slight irritation of the skin (painting with iodine) can cause proliferation without preceding degenerative changes makes this appear probable. But it is more probable that, in spite of the negative findings, slight tissue-changes of a degenerative nature do occur, and that through these the inhibitory influences are weakened.

Moreover, it must be noted that even the hypertrophy of muscles and glands following increased activity cannot be absolutely regarded as the direct result of a nervous or chemical stimulus, but rather must we assume that with the *increased labor there is an excessive consumption of cell-elements which excites regenerative processes*, the latter leading not only to a restoration of the parts lost, but also to an increased building-up of the cell-mass and formation of new cells.

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See also §§ 80–87.

§ 80. The **division of the nucleus and cell-body**, upon which process the formation of new tissue depends, may occur in the first place through **holoschisis** (Flemming), or **direct segmentation** (Arnold)—that is, through a transverse constriction of the elongated nucleus and protoplasm without an increase or characteristic grouping or movement of the chromatin elements of the nucleus. It appears, however, that the direct division of the nucleus leads to a new-formation of tissue—that is, to the production of cells which are able to form new tissue—only when it is connected with that form of cell-division known as **karyokinesis** or

FIG. 147. FIG. 148. FIG. 149.

FIG. 147.—Enlarged nucleus. Increase in the chromatin framework.

FIG. 148.—Thick, open skein, with segmentation of the threads into chromosomes; the nucleolus and nuclear membrane have disappeared.

FIG. 149.—Grouping of the completed chromosomes into a star- or wreath-form.

karyomitosis (Flemming) or as **indirect segmentation** (Arnold), which is characterized by an *increase of the* **nuclein** or **chromatin** (Flemming), *and a definite cycle of changes of form and movements on the part of the latter.*

Usually karyomitosis follows a typical course, as in the normal growth of tissue, but deviations from this are not infrequently seen in pathological new-formations.

A **resting necleus** consists of an outer covering, the *nuclear membrane*, and the *nuclear contents*. The latter is composed of a colorless *nuclear fluid* and the *nuclear substance*. To the nuclear substance belong the *nucleolus* and *scattered granules and threads* which often form a *framework* staining with nuclear stains.

When the nucleus undergoes **division**, there usually occurs in the first place, an *increase of the chromatin*, and the chromatin *framework* becomes more distinct (Fig. 147). The nuclear substance then forms a *close skein*, which with the disappearance of the nuclear membrane and the nucleolus becomes changed into an *open skein* with thick threads (Fig. 148), whose individual components divide themselves into *nuclear segments* (Hertwig) or *chromosomes* (in man these number eighteen) (Figs. 148, 149).

These segments then group themselves in the equatorial plane of the nucleus with their angles directed toward the centre, forming, when viewed from the polar aspect, a wreath-like figure (Fig. 149), and later a star-like figure, lying in the equatorial plane, which has been designated the mother-star (Figs. 150, 151), or the equatorial plate (Flemming).

Sooner or later *two poles* become visible in the so-called polar field—that is, two extremely small spherules, which are known as the *polar* or *central corpuscles* or the *centrosomes*. At first these lie closely together,

but later separate from each other and act as centres about which the nuclear elements group themselves. Between these there is formed the *nuclear spindle* (Figs. 152, 153) which consists of fine threads which do not stain with nuclear stains, and converge in the polar corpuscles. In

FIG. 150. FIG. 151. FIG. 152.

FIG. 153. FIG. 154. FIG. 155.

FIG. 150.—Completely developed mother-star; polar view.

FIG. 151.—Mother-star; equatorial view.

FIG. 152. Stage of metakinesis. Single loops visible, their angles pointed toward the pole; delicate spindle-figure within the nucleus.

FIG. 153.—Daughter-star; side view (nucleus barrel-shaped); spindle-figure in the nucleus and the radial arrangement of protoplasm are visible.

FIG. 154.—Daughter-stars separated: the upper one presenting polar aspect, the lower one a side view.

FIG. 155.—Daughter-skein with fine threads (above), and with lattice-work (below). Completed division of the protoplasm.

the neighborhood of the polar corpuscles themselves the granules of the protoplasm present a radial arrangement, giving rise to figures (Fig. 153) which are known as *ray-figures, stars,* or *attraction-spheres.* In the following stage of division of the nucleus, a movement takes place among the chromosomes leading to the formation of loops, whose angles are directed toward the pole. Later the loops divide in halves which, following the direction of the spindle-fibres, move toward the poles and form two stars (Figs. 152–154) which are known as *daughter-stars.* From the star-figures the daughter-star passes successively through the thick-skein and then the fine-skein stage (Fig. 155, upper part) which finally changes into the nuclear *framework* (Fig. 155, lower part). During the later stages of the process of division a new nuclear membrane is formed.

In the stages of the segmented skein, or later as may be seen in the

large nucleated cells of cold-blooded animals, there occurs a *longitudinal splitting* of the *chromosomes* (Fig. 156). In the change of position of the chromosomes known as *metakinesis* the halves of the split threads sepa-

FIG. 156. FIG. 157.

FIG. 156.—Mother-star, with chromosomes split longitudinally. (After Rabl).

FIG. 157.—Metakinesis. The halves of the chromosomes are separating from each other and turning toward the poles. (After Rabl.)

rate from each other (Fig. 157) so that each daughter-star receives half of the substance of each chromosome.

The **division of the cell-protoplasm** usually takes place at the time the daughter-star changes into the ordinary nuclear condition, and consists in a constriction and separation of the protoplasm (Fig. 155). It is probable that a complicated interrelationship exists between the nucleus and cell-protoplasm; but the nucleus is to be regarded as *the more highly organized substance, as the centre of cellular potentiality.* The *nuclei are also the bearers of heredity*, while the protoplasm governs the relations of the cell with the outer world.

Variations from the typical karyokinesis may consist in the first place in the occurrence of a *pluripolar division* in place of the bipolar, so that two to six or more nuclear spindles and a correspondingly increased number of equatorial plates (Fig. 158, *a*) may be formed. Further, in place of the simple mother-star there may be formed a complicated figure out of the chromatin loops, from which several daughter-stars may be evolved. Not infrequently there occur *asymmetrical divisions of the nucleus* (Fig. 158, *b*, *c*), particularly in tumors, but occasionally also in regenerative or inflammatory new-formations of tissue.

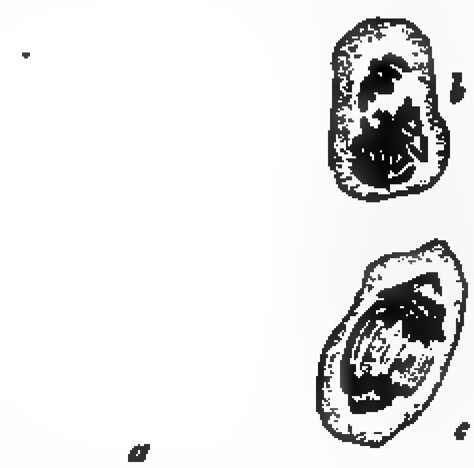

FIG. 158.—*a*, Pluripolar division-figure; *b*, *c*, asymmetrical division-figures.

There also not infrequently occur divisions of the nucleus which are characterized by *abnormal size, abnormal richness in chromatin,* and *manifold variations of form.* As types of such division are the large oval or bean-shaped (Fig. 159), knobbed or convoluted, lobulated and branched (Fig. 160), wreath-shaped, linked, basket-shaped (Fig. 161), and otherwise-shaped nuclei. Finally, there are occasionally found in the cells more or less extensive, indistinctly-outlined heaps of granular and lumpy chromatin (Fig. 162).

Such nuclear forms, with the exception of the polynuclear leucocytes, e found particularly in the cells of the bone-marrow, spleen, and mph-glands, and also in tumors which arise from the bone-marrow or riosteum, but have been also observed elsewhere, particularly in sarmata. Certain of these forms are appearances due to contraction, and ve nothing to do with cell-division. In other cases these changes of e and form precede a division of the nucleus through constriction of rtain portions, this process occurring sometimes with, sometimes witht an increase of the chromatin-substance. Arnold has designated the vision by constriction with increase of the chromatin as *indirect fragntation*, that without such increase as *direct fragmentation*. Indirect agmentation differs from mitosis or indirect segmentation in the lack

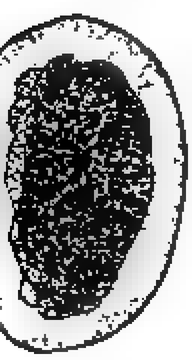

FIG. 159. FIG. 160. FIG. 161. FIG. 162.

FIG. 159.—Cell with oval, slightly knobbed giant-nucleus, rich in chromatin.

FIG. 160.—Cell with lobulated giant-nucleus. FIG. 161.—Cell with basket-shaped giant-nucleus.

FIG. 162. Cell with large masses of chromatin. All these cells from a sarcoma of bone. (*Stroebe, träge von Ziegler*, VII.)

an orderly arrangement of the chromatin in threads and in the irregurity with which the separation of portions of the chromatin results in w nuclei.

Variations in the division of the cell-protoplasm occur most freently, either in a *total failure of the protoplasm to divide* after the division of the nucleus has taken place, or in the *delayed division* after that the nucleus. These enomena are obrved in both mito- and amitotic divisn of the nucleus, d lead to the foration of **multinuear giant-cells** (Fig. 163), which are signated as **plasodial giant-cells.**

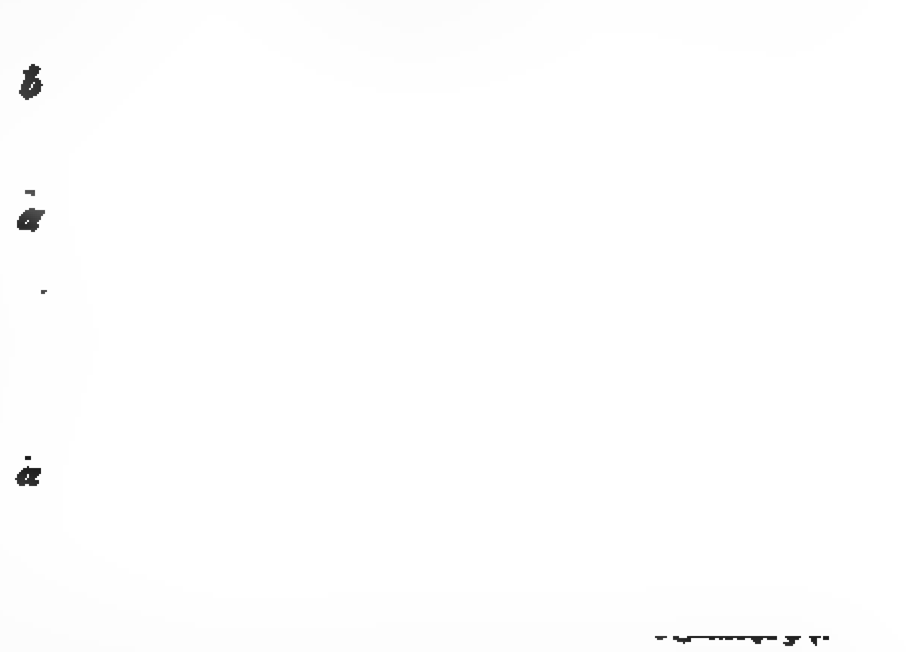

FIG. 163.—Proliferating adipose tissue from the subcutaneous panniculus, twenty-six days after cauterization with trichloracetic acid (formalin, hæmatoxylin). *a*, Multinuclear fat-cells; *b*, proliferating connective tissue. × 300.

Cells of the spleen d bone-marrow and tumors arising om the bones show is phenomenon with pecial frequency. roliferating fat-cells kewise often form

multinuclear giant-cells (Fig. 163, *a*). Besides this form of multinuclear giant-cell there also occur those formed by the *confluence of cells*, which are known as **syncytial giant-cells.** (Compare also the sections on Inflammation and Tuberculosis.)

The significance of the nuclear corpuscles (nucleoli) is still a matter of dispute. *Flemming* and *Pfitzner* believe that they are different from the nuclear framework, while others regard them as much-thickened nodal points of the fibrils of the framework. In what way they are again formed after the division of the nucleus is not known.

The spindle-figure, whose fibres stain but slightly with nuclear stains, is derived, according to *Flemming* and *Hertwig*, from the achromatic substance of the nuclear framework, while *Strasburger* believes that it arises from the cell-protoplasm.

The *centrosomes* or *polar corpuscles*, which are always present in nuclear segmentation, are found also in resting-nuclei; but up to the present time they have been demonstrated only in a part of the cells, most frequently in lymphocytes and the giant-cells of the bone-marrow. At the same time the investigations of *von Kölliker*, *Flemming*, *M. Heidenhain*, *Boveri*, and others make it probable that the centrosomes are present in all cells, lying sometimes in the nucleus, sometimes in the protoplasm, where on account of their small size they can be demonstrated only with difficulty. (The centrosomes do not stain with the ordinary nuclear stains, but with acid aniline dyes, as acid fuchsin, safranin, and with iron-hæmatoxylin.) Whether they are elements of the protoplasm or of the nucleus has not yet been decided. According to *van Beneden*, *Boveri*, and *Rabl*, the mitosis of the nuclear substance is to be referred to a direct drawing-apart, starting from the divided centrosomes and brought about by the agency of the achromatic fibres. According to *M. Heidenhain*, the central corpuscles are sharply circumscribed granules which possess the power of assimilation, of growth, and of multiplication by budding, whereby they are accustomed to form groups. Either alone or united in groups, they can form the central point of insertion of a system of contractile fibres (spindle-figures, microsome rays), and consist of a specific substance (in a chemical sense) which is not present elsewhere in the cell.

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The Processes of Hyperplasia and Regeneration in the Various Tissues.

§ 81. The morphological changes in the **regeneration and hyperplasia** epithelium are relatively simple. The karyomitoses (Fig. 164, *a–d*) ow for the chief part a typical course. The division of the protoplasm kes place either in the later stages of the process of nuclear division or

follows after the same. Giant-cells may arise through failure of protoplasm to divide.

Epithelium arises only from epithelium, and, moreover, the differ varieties of epithelium do not pass over into one another. It is to noted, however, that under certain conditions—for example, in case inflammatory irritation of long standing—the regenerating epithelium may change its character so that pavement epithelium may occasionally be developed in places which originally possessed stratified ciliated columnar epithelium. This may occur, for example, in the case of cicatrization of ulcers in the trachea. Defects of ciliated columnar epithelium are in the first place repaired by low columnar or flat cells which later become changed into high columnar cells.

FIG. 164.—Regenerative proliferation of the epitheli bile-ducts, in the neighborhood of a wound of the liver five da Flemming's solution, safranin). *a*, Enlarged nucleus thelial cell, with increase of chromatin; *b*, epithelial cel mother-skein; *c*, epithelial cell with mother-star; *e*, epi cell with daughter-skein; *f*, connective-tissue cell with dau star. × 400.

Small losses of substance in the superficial epithelium are usu quickly replaced through regenerative growth of the neighboring (Fig. 165, d, d_1, d_2). In such cases it may be seen that the epithel bordering upon the defect quickly pushes over the denuded surface begins to proliferate. The division of the nucleus and cell-protopl takes place not only on the edge of the defect, but also at some dista from it. In the intestine the loss of the superficial epithelium is quic made good by a proliferation of the epithelial cells situated in the parts of the crypts of Lieberkühn. Likewise glandular epitheliu for example, in the liver or kidneys—is quickly restored after loss, vided the structure of the tissue—that is, of the basement membr

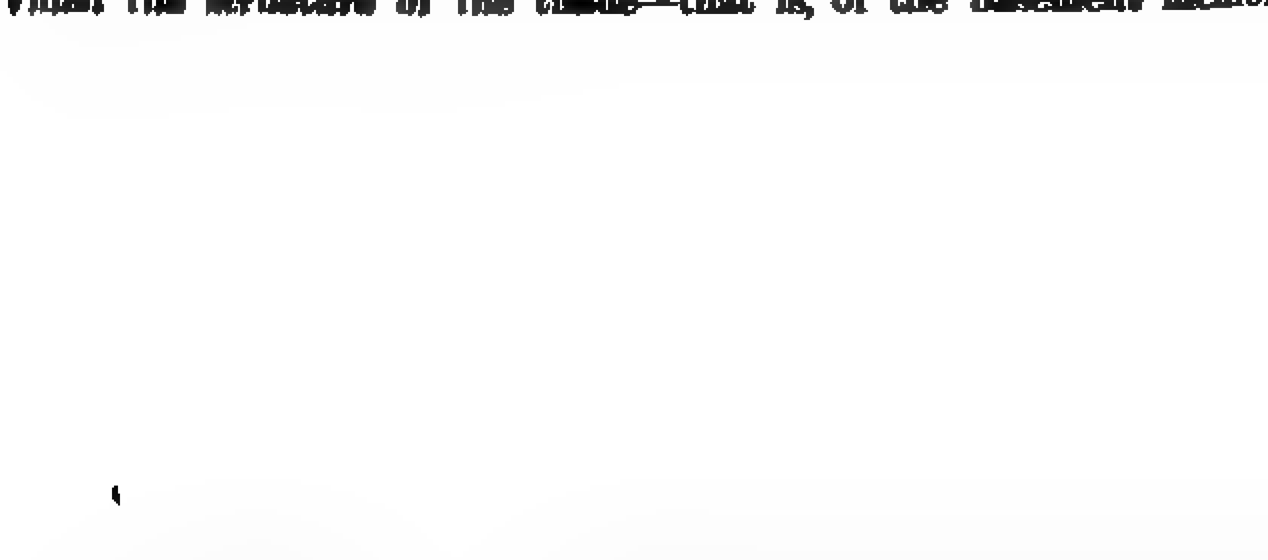

FIG. 165.—Healing of blister caused by a burn (alcohol, alum-carmine). Section through the sk cat's paw forty-eight hours after the production of a blister. *a*, Horny layer; *b*, rete Malpighii; *c*, ro *d*, newly formed epithelium; d_1, d_2, newly formed epithelium already differentiated into different l *e*, old, degenerated epithelium; *f*, pus-cells; *g*, exudate; *h*, sweat-glands. × 25.

upon which it rests—is not changed. After destruction of liver-ti both liver cells and the epithelium of the bile-ducts (Fig. 164) pr

e, and the cell-division attendant upon an injury to the liver may end to a relatively great distance from the wound. Experimental nds of the liver heal through the formation of connective tissue, into ch only offshoots of the bile-ducts penetrate, while a local reproduc- of liver-tissue does not take place. Likewise, in the kidneys, testi-, thyroid, and ovary the local production of glandular tissue in the nective-tissue scar is very slight or wholly wanting, and does not l to the formation of functionating tissue. In the salivary and mu-s glands, on the other hand, there occurs a branching of the gland-ts, and a new-formation of glandular alveoli.

When portions of the mucosa and submucosa of the intestine are lost result of ulcerative processes, there occurs during the process of ling a glandular proliferation, which, according to the nature of the ect, forms partly typical, partly atypical (Fig. 144, *i*) glands which w into the submucosa. The new gland-formation takes its start from old glands, whose epithelium pushes over the edge and base of the er (Fig. 144, *g*, *h*) and also lines any depressions which may happen be present (*k*). In a similar manner ulcerative defects of the stomach cosa are again made good; and even extensive ulcers may become ered over with a gland-containing mucosa, although the glands do for the most part show a typical development—that is, are not trans-ned into characteristic gastric glands.

The epithelial portions of the uterine mucosa which are in part lost, physiological process, during menstruation and parturition, and are rward replaced, may be restored in a similar manner in the healing athological defects of the endometrium. The new-formation of epi-ium takes its origin from the glandular remains.

Compensatory hypertrophy of a kidney or liver, as the result of the of kidney- or liver-tissue, is brought about through the *formation of gland-cells, and the enlargement of existing renal tubules,* or *liver-rods ectively*. After extirpation of one kidney the beginnings of compen-ry hypertrophy are recognizable even on the third day, by the ap-rance of division figures in the epithelium of the urinary tubules; there then follows a further proliferation, continuing for some time, he epithelium of the uriniferous tubules and glomeruli as well as of cells of the vessel-walls, as a result of which all the parts become arged. In the liver the lobules are enlarged, but no new-formation hese occurs.

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§ 82. The **new-formation of blood-vessels** plays a very important rôle in hyperplasia of the most varied tissues. If connective tissue, bone, or glandular tissue is to be reproduced in any considerable amount, the new-formation of blood-vessels is essential, since it is only through these that sufficient nutrition can be brought to the growing tissue.

The development of new blood-vessels takes place through the **formation of offshoots** from the sides of the walls of preëxisting vessels (Fig. 166). In the vessel-wall there occurs a **proliferation of cells, particu-**

y **of the endothelium** (Fig. 167), in which the division of the leus occurs by **karyomitosis.**

As the first step in the formation of a new vessel, there is seen on the er side of some capillary loop a tent-like elevation which terminates fine protoplasmic thread (Fig. 166, *a*), standing out from the vessel, gradually becoming longer and longer, while the granular mass like-

'IG. 166.—Development of blood-vessels by formation of offshoots; from preparations taken from in- matory granulations. *a*, *b*, *c*, *d*, Different forms of offshoots, some solid (*b*, *c*), others becoming hol- *a*, *b*, *d*), some simple (*a*, *d*), some branching (*b*, *c*), some without nuclei (*a*, *d*), some with nuclei); *d*, offshoot to which fibroblasts have applied themselves.

e grows out at the same time. There is thus formed at the beginning *lid granular arch of protoplasm, which ends in a protoplasmic thread* (*a*), l after a certain time comes to contain nuclei. This thread may netrate into another vessel, or may unite with some other arch which neets, or finally may return to the same vessel from which it started.

Further, from the solid arch itself new secondary arches may spring g. 166, *b*, *c*), or at its end there may be formed a club-shaped swell- (*c*).

The originally solid arch becomes hollow after a certain time (*b*, *a*) ough the liquefaction of its central part, and the space thus formed ner immediately or very soon comes to communicate with the lumen the blood-vessel (*a*), or else there is developed from within the vessel extension of the vessel-lumen into the arch. The blood of the mother- sel finds its way at once into the cavity of the daughter-vessel and lens it. As the hollowing-out process constantly advances and ex- ds to the point of entrance of the protoplasmic arch into another od-vessel, there is finally formed a new capillary loop permeable for od.

Immediately after the opening of a way for the blood the capillary e possesses a homogeneous wall. After a certain length of time the toplasm groups itself about the nuclei, which have in the mean time

divided and multiplied in the wall, so that ultimately the capil comes to be made up of flattened endothelial cells. As Arnold shown, the boundaries of the individual flattened endothelial cells be made visible through the injection of a solution of silver into the sel. At this time the wall for the greater part appears much thicke partly from the proliferation of the cells of the vessel-wall, but partly from the fact that formative cells from the neighborhood themselves upon the surface of the young vessel (Fig. 166, *d*), a themselves to the wall, and so strengthen it.

At the time of the formation of the offshoots, the endothelial ce the capillaries are swollen, so that they form cells rich in protopl which often in proliferating tissues reach such a size that the cross tion of a capillary looks not unlike a gland-tube lined with epithe (Fig. 168, *d*). At the same time division-figures appear in the e thelium (Fig. 167, *a–c*), and later the division of the nucleus and protoplasm takes place.

Just in what relation this proliferation stands to the formation of offshoots is not yet clearly understood; but doubtless the latter sp from proliferating cells and represent cell-processes of the same. The proliferation of endothelium, on the other hand, does not always lead to a new-formation of vessels, but may result only in a thickening of the vessel-wall and finally in an obliteration of the lumen.

In the transformation of newly formed capillaries into arteries and veins—a change which must always occur in the case of extensive new-growths—the increase of tissue is the result of the continued proliferation of the cells of the vessel-wall. The *muscle-fibres* first appearing in the outer wall of the capillary tube are (Mayer) finely-branched cells whose nuclei lie parallel to the long axis of the capillary and whose processes surround the endothelial tube. After about fourteen days *elastic fibres* may also appear in new-formed vessels (arteries).

FIG. 167.—Two vessels papillary body, whose thelial cells are in pro proliferation (six days painting the back of th with tincture of iodine. ming's solution, safrani picric acid). *a*, Nucleu chromatin framework. skein-forms; *c*, mothe *d*, connective-tissue ce nuclear division-figure lymphocytes. × 350.

It is difficult to decide whether the *new-formation of blood-vessels* is intracellular through the hollowing out of the solid buds of a single cell or whether it is intercellular through the formation of a space between two cells. The offshoots from the sides of the vessel-wall or from the end of the vessel give the impression of solid cell processes, but the possible participation of the protoplasm of two cells in the forma of such processes cannot be excluded.

The *new-formation of lymph-vessels* in new connective tissue is intercellular.

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§ 83. The **connective-tissue structures** are almost all capable of both hyperplastic and regenerative proliferation. This is especially true of unformed and formed connective tissue, the periosteum and the endosteum; while cartilage possesses but a slight regenerative capacity, and fully developed bone none at all. Usually proliferating fibrous connective tissue gives rise to fibrous tissue, both in the case of independent formations of connective tissue and in the supporting tissue of the glands, lungs, lymph-glands, and brain. The periosteum, bone-marrow, perichondrium and cartilage produce in addition to fibrous connective tissue and marrow-tissue also cartilage and bone.

Hyperplastic and regenerative proliferations of the connective tissues are ushered in by *cell-division* in the course of which the karyomitoses, described above (Figs. 164, *f*; 167, *d*; 168, *b*, *c*), occur.

FIG. 168.—Proliferating periosteum, four days after fracture of a bone (Flemming's solution, hæmatoxylin). *a*, osteoblasts with large nuclei; *b*, osteoblast with division-figure; *c*, two cells shortly after division, showing thread-skein in nucleus; *d*, blood-vessel with proliferating endothelium; *e*, endothelial cell with nuclear division-figure; *f*, large lymphocytes; *g*, small lymphocytes. × 350.

After injuries of the tissue these proliferations begin very soon, as, for example, in wounds of the skin, or in fractures of the bones; in the latter case even as early as the second day single cells of the periosteum have become enlarged and show division-figures. Besides mitoses, direct division of the nuclei also takes place.

When only a few cells are destroyed in the event of an injury to the tissue newly formed cells replace those destroyed without the occurrence of any marked structural changes in the tissues. If, on the other hand, under pathological conditions, a considerable amount of new tissue is produced within a short time, the proliferating cells form an **embryonic tissue** consisting essentially of cells, blood-vessels, and a somewhat fibrillated ground-substance (Fig. 168). The extent of such formation naturally varies greatly and is dependent partly upon the capacity of the tissue for proliferation, and partly upon the lesion leading to the proliferation.

Proliferating cells are always larger than the cells of fully developed and resting connective tissue which are relatively poor in protoplasm. They contain large, bladder-like nuclei with nucleoli, and for the greater part only one or two nuclei (Figs. 168, 169), though multinuclear cells (Fig. 169, c_1), the so-called *giant-cells*, also occur. In association with the

enlarged tissue-cells there are always found after a more marked tissue lesion exudative cells arising from the blood-vessels (Figs. 168, *g, f,* and 169, *a*, a_1) which take no part in the formation of the new tissue (see § 95).

Since all these cells are the antecedents of the future tissue they are designated as **formative cells**, those giving rise to fibrous connective

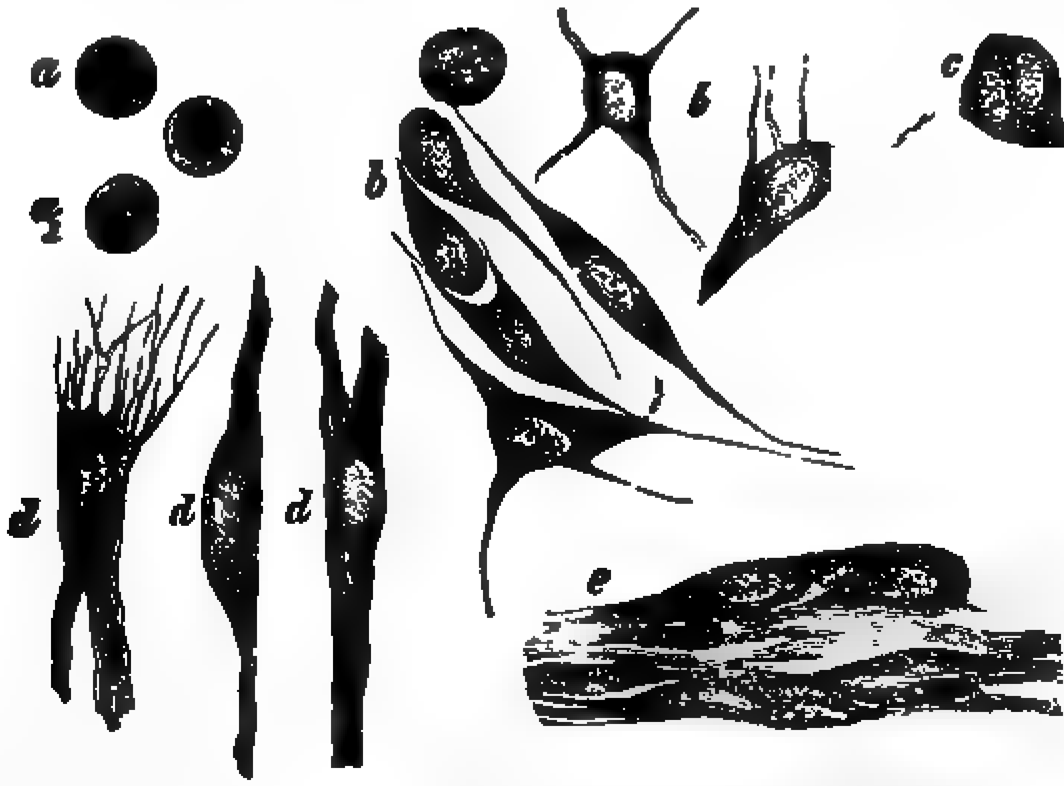

FIG. 169.—Isolated cells from a granulating wound (picrocarmine). *a*, Lymphocyte; a_1, polynuclear leucocytes; *b*, different forms of mononuclear fibroblasts; *c*, formative cell with two nuclei; c_1, multinuclear formative cells; *d*, fibroblasts in stage of connective-tissue formation; *e*, fully developed connective tissue. × 500.

tissue are called **fibroblasts** (Figs. 169, *b, c, d. e*; 170, *a*), while those forming cartilage and bone are known as **chondroblasts** (Fig. 172, *a, c*) and **osteoblasts** (Fig. 168, *a, b, c*) respectively.

The shape of the formative cells varies greatly (Fig. 169, *b, c, d, e*), and is dependent, partly upon intrinsic causes—that is upon spontaneous changes of form—partly upon the influence of the environment, which under certain conditions compels the cells to take certain definite forms. The cells producing connective tissue usually present the greatest variety of form.

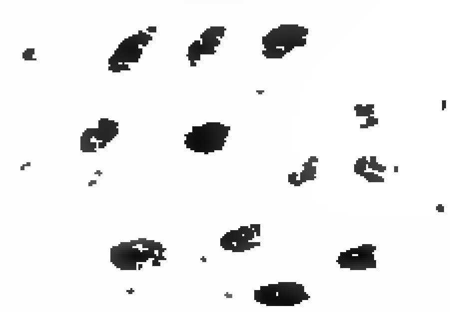

FIG. 170.—Development of connective tissue from fibroblasts (Müller's fluid, picrocarmine). *a*, Fibroblasts; *b*, hyaline ground-substance with scattered fibrillæ; *c*, fibroblast with adjacent fibres. × 400.

When **connective tissue** is developed from a cellular embryonic tissue, either *fine fibrillæ* (Fig. 169, *d, e*) appear at once in certain parts of the cell-protoplasm, or there is formed first a *homogeneous intercellular substance* (Fig. 170, *b*) in which the fibrillæ later appear. The formative cells at the same time diminish in size, and come to lie, for the most part, in small clefts (Fig. 169, *e*) in the ground-substance.

Elastic fibres first appear in newly formed connective tissue at a late stage, about three weeks at the earliest, and at the beginning form very fine fibrillæ, which in part (Fig. 171, *b*) represent processes of older thicker fibrillæ (*a*) and in part arise independently. They represent a differentiation product of the fibrillary ground-substance and have no relation

to the cells. In so far as can be determined, they are formed through the union of small granules of elastic substance.

They develop most abundantly in newly formed connective tissue in the blood-vessels and in the skin, but such a new-formation of elastic

FIG. 171.—Scar of the skin, two years old, showing newly formed elastic fibres (alcohol, orcein). *a*, Corium with normal elastic fibres; *b*, scar with newly formed elastic fibres. × 300.

fibres occurs also in other regions, as, for example, in connective-tissue proliferations inside of glands, serous membranes, etc.

In the development of **hyaline cartilage** there appears between the cells a hyaline basement-substance (Fig. 172, *f*), while the *chondroblasts* (*c*) at the same time assume a more rounded form (*d*). In time the ground-substance increases, the chondroblasts grow smaller and come to lie in rounded cavities whose walls are denser than the rest of the ground-

FIG. 172.—Periosteal formation of cartilage in a fracture five days old (Flemming's solution, haematoxylin, glycerin). *a*, Cellular embryonic tissue; *b*, cartilage; *c*, proliferating periosteal chondroblasts; *d*, cartilage-cells; d_1, d_2, nuclear division-figures in cartilage-cells; *e*, ground-substance of embryonic tissue; *f*, ground-substance of the cartilage; *g*, capsule of cartilage-cells; *h*, proliferating endothelium of a blood-vessel. × 320.

substance and later form the part of the basement-substance called the *cartilage-capsule* (*g*).

In the development of **bone** from cellular embryonic tissue there appears between the formative cells a dense homogeneous or fibrillated

basement-substance (Figs. 173, *e, f*; 174, *c*) forming an **osteoid tis**
which later on becomes impregnated with lime-salts and thereby tra
formed into **bone.** When the ground-substance between the osteobl

FIG. 173.—Endosteal formation of bone from masses of osteoblasts (Müller's fluid, picric acid, ha toxylin, carmine). Preparation from the inner callus of a fourteen-day old fracture of the fibula of a twenty-five years of age. *a*, Fat-cells of the endosteum; *b*, endosteum containing no fat; *c*, scatt osteoblasts; *d*, groups of osteoblasts; *e*, first step in the formation of the ground-substance of bone; *f* veloping trabeculæ of bone; *g*, layer of osteoblasts lying upon the newly formed trabeculæ of bone blood-vessel. × 150.

is already of a loose fibrillar nature (Fig. 173, *d*) the transition i
osteoid tissue is brought about through a thickening of the ground-s
stance (*e, f*). The *osteoblasts* come to lie in irregular spaces furnish
with processes (Figs. 174, *c*; 175, *b*), and are then usually known
bone-corpuscles. In extensive development of cellular embryonic tis

FIG. 174.—Formation of osteoid trabeculæ from the proliferating periosteum. Preparation fro fourteen-day old fracture (Müller's fluid, picric acid, hæmatoxylin, carmine). *a*, Fibres belonging to outer periosteum; *b*, embryonic tissue; *c*, osteoid tissue; *d*, cartilage; *e*, bone-marrow. × 75.

the change into bone is limited to certain parts of the tissue, so th
within the embryonic tissue trabeculæ (Fig. 174, *c*) are formed, whic
so long as they do not undergo full development into bone and do n

become calcified, are called **osteoid trabeculæ.** The embryonic tissue (*b*) lying between becomes changed into **marrow-tissue** by the cells becoming united to each other through processes, while between them there appears a fluid basement-substance, in which round-cells later appear embedded. If only a little bone-tissue is to be formed and deposited upon old bony trabeculæ, the *osteoblasts* (Fig. 175, *c*) arrange themselves upon the surface of the latter, and these later on produce bone (*b*) in the manner described above, which appears as a new bony lamella.

Fibrillated connective tissue, bone, and cartilage are closely related to each other and one may, therefore, be easily transformed into the other (see § 88).

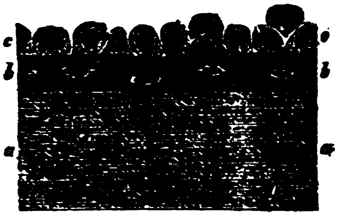

FIG. 175.—Formation of bone, through deposits made by osteoblasts upon the surface of old bone (Müller's fluid, picric acid, hæmatoxylin, carmine). *a*, Old bone; *b*, newly formed bone; *c*, osteoblasts. × 200.

Mucous tissue arises from embryonic tissue through the formation of a mucin-containing, homogeneous, gelatinous basement-substance between the cells which at least in part become united through processes to form a network.

Lymphadenoid tissue can develop from embryonic tissue through the formation of a supporting reticulum from a part of the cells, while lymphocytes gather in the meshes of this network, the spaces of which contain lymph. In *injured lymph-glands*, the cells of the reticulum proliferate and form *ordinary fibrous tissue;* a reticular development of this connective tissue into lymphadenoid connective tissue either does not take place at all or but to a very slight degree.

Spleen-tissue is not formed anew after injury to this organ; the wound heals through ordinary *cicatrization.* Compensatory hypertrophy does not take place after the removal of large portions of the organ.

Fat-tissue arises through the taking up of fat into the cells of embryonic tissue, mucous tissue or fibrous connective tissue, the cells becoming changed into fat-cells through the confluence of the fat-droplets which they take up.

The **basement-substance** of the tissues described above is a **product of the protoplasm of the formative cells.** Whether in its formation portions of the cell-protoplasm are changed directly into intercellular substance, or whether they secrete the latter, or separate it from the intercellular fluid, is often a difficult question to answer; but it is probable that only the first two methods of formation occur.

Fibrillar connective tissue can develop from any of the connective tissues possessing the power of proliferation, but there must first be formed an intermediate stage of embryonic tissue.

Bone arises chiefly from the periosteum, perichondrium, and endosteum, but may also develop from other connective-tissue substances, as, for example, from the intermuscular connective tissue and from the connective tissue of the blood-vessels.

Cartilage arises chiefly from proliferating perichondrium, periosteum, endosteum, and cartilage itself; but may also be developed from other connective tissues, as, for example, in the connective tissue of the testicle and parotid. The cartilage-cells near a lesion may under certain circumstances proliferate and form a large-celled embryonic tissue, but this does not reach any great size. In the proliferation of cartilage-cells within cartilage the cell-multiplication and new-formation of cartilage occur in the same way as in the physiological proliferation of this tissue. Very often the newly formed cartilage is only a transitory tissue, and is soon transformed again into bone and marrow-tissue, or into connective tissue.

New *lymphadenoid tissue* may, under pathological conditions, arise either from lymphadenoid tissue or fat-tissue (*Bayer*) or from fibrillated connective tissue. It is formed from the latter most frequently in the connective tissue of the mucosa and sub-

mucosa of the intestinal tract, as well as in the glandular organs; rarely in the int muscular connective tissue. New hæmolymph-nodes are formed in adipose tis after splenectomy (*Warthin*).

Mucous tissue may develop from any proliferating connective-tissue substance, b rarely appears in large masses, and is usually a transitory form passing over either in fat or connective tissue.

Fat tissue develops particularly in those regions normally containing fat, but o curs also at times in other places, for example, in the reticular connective tissue atrophic lymph-glands, in the perimysium internum of atrophic muscles, etc

The close relationship of the connective-tissue substances to each other enables t different forms to pass from one to another without the need of an intermediate st of embryonic tissue produced by proliferation. Further details in regard to this po are contained in § 88.

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§ 84. **The new-formation of the red blood-cells or erythrocytes** occurs through the mitotic division of nucleated young forms of red cells known as **erythroblasts** (Bizzozero, Neumann, Flemming). In the adult this new-formation is restricted to the bone-marrow, and this is true

also of other mammals, birds, reptiles, and tailless amphibians, while the tailed amphibians and in fishes the spleen also takes part in the pr ess. In embryonic life the new-formation and increase of the red blo cell takes place throughout the entire vascular system, but later it comes restricted to the spleen, liver, and bone-marrow, and finally the last alone.

The entrance of the red blood-cell into the circulation takes pl after the loss of its nucleus.

In the increased new-formation of red blood-cells following a loss blood, as well as in severe chronic anæmias and leukæmia, nucleated blood-cells may appear in the circulating blood outside of the bo marrow. The fatty marrow may thereby take on again in part character of the splenoid marrow, this change being accomplished by dilatation and congestion of the blood-vessels with an increase in colorless and red cells of the marrow, while the fat present in the su porting reticulum disappears.

The **new-formation of the colorless cells of the blood and lym** grouped together under the broad term **leucocytes** occurs essentially the lymphoid tissue of the lymph-glands, mucous membranes, sple thymus, and bone-marrow; but leucocy within the blood- and lymph-vessels a tissue-spaces outside of these organs m also divide, and well-defined foci of pro eration may thus be formed. The mo nuclear cells, known as *lymphocytes*, deve chiefly in the first-named regions, a numerous karyomitoses (Fig. 176) are c stantly found in the so-called germi centres. The *polymorphonuclear* or *poly clear leucocytes* and the *eosinophile cells*, the other hand, are formed in the bone-m row. Whether the large cells with cl nuclei known as *mononuclear leucocytes*, a the *transition-forms* with horseshoe-sha nuclei developing from the latter, are formed in the bone-marrow is doubtf They can also be regarded as more ful developed lymphocytes.

FIG. 176.—Section from the germinal centre of a mesenteric gland (after Flemming). *a*, Large, *b*, small lymphocytes; *c*, karyomitoses; *d*, direct nuclear division or nuclear fragmentation; *e*, cells containing near the nucleus "tingible bodies" and small yellow pigment granules, whose significance is unknown. × 400.

A pathological increase of the colorl cells (leucocythæmia) may take place through an increased emigrat of cells from the formative tissues without an actual increase in c production. A long-continued persistence of such an efflux presuppo an increased production also.

A transitory leucocythæmia is designated *leucocytosis*, while a per nent one is called *leukæmia*. The former is characterized by an incre in the neutrophile polynuclear leucocytes, rarely by increase in lymphocytes. Two forms of leukæmia are distinguished: a *lympha* in which the lymphocytes are increased, and a *myelæmia* or *mye leukæmia*, characterized by the appearance in the blood of *myelocytes*, mo nuclear cells with neutrophile granulation arising in the bone-marr (See Pathology of the Blood.)

The polynuclear leucocytes escaping from the circulatory system sh no progressive changes. The *mononuclear cells of the blood* may, on contrary, appear in various forms known as *epithelioid cells*, *plasma-c*

klasmatocytes, and mast-cells. With reference to their power to give rise to different forms of cells they may be designated as *polyblasts* (Maximow). (See also chapter on the Inflammatory New-formation of Tissue.)

According to *Neumann*, the young forms of the red blood-cells multiply in the lymphoid marrow. *Bizzozero* and *Denys* hold that this new-formation takes place normally only within the marrow-vessels, and the new-formation of the red blood-cells is completed within the same. The *change of the nucleated cells into non-nucleated ones* is brought about, according to many writers, through a disappearance of the nucleus. According to *Rindfleisch, Howell, Malassez*, and *Maximow*, the nucleus is extruded. According to *Maximow*, there may be distinguished in the protoplasm of erythroblasts possessing old pyknotic nuclei a granular area surrounding the nucleus and a homogeneous peripheral substance. After the extrusion of the nucleus the inner granular substance, which stains with neutral red and other dyes, is at first preserved, but vanishes with the ripening of the capsule.

According to *Bizzozero*, the young forms of the red blood-cells are cells of an individual type that are always hæmoglobin-containing and have no colorless ancestors. *Denys, Löwit, Howell*, and *Pappenheim*, on the contrary, hold that they arise from nucleated hæmoglobin-free, colorless cells (basophile leucocytes, *Pappenheim*) believed by *Denys* to increase within the marrow-vessels; while *Löwit* thinks that the colorless antecedents of the red cells, which divide by mitosis and which he calls *erythroblasts*, occur in the lymph-glands and spleen as well as in the marrow, and lie both within the vessels and in the meshes of the reticular tissue.

Flemming, who agrees with *Bizzozero* concerning the hæmoglobin-content of the nucleated young forms of red cells, is inclined to assume that the young forms present in later life are the direct descendants of the young forms of the embryonic period. *Neumann* holds that this hypothesis is not sufficient to explain all the phenomena of later life; as, for example, the replacement of the fatty marrow which contains no nucleated red cells by blood-forming lymphoid marrow, and the formation of red blood-cells in such newly-developed marrow. He finds himself forced to the conclusion that either a development of the nucleated red cells takes place from the leucocytes of the blood which after birth are carried to the marrow through the arteries, or that they arise from the tissue-elements of the bone-marrow.

Petrone believes that the red blood-cells of the mammals are only apparently non-nucleated, and that it is possible by means of especial methods of fixation and staining to render the nucleus visible. This invisible nuclear substance is iron-containing and shows an affinity for acid stains, while the nucleus of the erythroblasts stains with basic dyes.

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§ 85. The **new-formation of transversely striated muscle-fibres** takes its start from portions of old muscle-fibres; and although, after injury to a muscle, the intermuscular connective tissue may be excited to active proliferation, there is formed in consequence only connective tissue, or probably also the sarcolemma of new fibres, but never new contractile substance.

The first signs of a formative activity of the muscle-fibres after injury appear in the muscle-nuclei, in that these become elongated and then divide into a varying number of fragments. Even on the second day there may occur mitotic division (Fig. 177, *a*, *b*) of the muscle-nuclei. This form of division seems to be the only way in which multiplication takes place, and under favorable conditions it occurs very actively after the second day.

The behavior of the contractile substance of the muscle differs very markedly according to the nature and extent of the injury. In the case

of traumatic, toxic, and anæmic injuries it suffers a fragmentation into larger and smaller portions, so that the muscle-cells come to lie in spaces of varying size between the detritus of the muscle-fibres. Crushing and tearing can bring about a wide separation of the parts of the contractile substance. The ends of the pieces of muscle-fibres, in such a case, may be conical, oblique, transverse, or torn in an irregular edge, but not infrequently after a short time the ends become split into two or more pointed filaments (Fig. 177 *a*).

The mitotic division of the muscle-nucleus takes place, not only in nuclei that rest upon living fibres (*a*), but also in the muscle-cells lying free in the spaces between the separated muscle-fibres (*b*); and in both places leads to the production of large multinuclear cells, which form multinuclear protoplasmic masses on the ends of the muscle-fibres (*e, f*) as well as on the body of the fibres (*c*). Into these masses the trans-

FIG. 177.—Portions of muscle-fibres showing regenerative proliferation, from muscle-wounds of different ages (Flemming's, safranin). *a*, Pointed ends of the split stump of a muscle-fibre, with nuclear division-figures, three days after laceration of the muscle; *b*, proliferated muscle-nuclei transformed into cells rich in protoplasm, one of which is in process of mitotic division; *c*, piece of a muscle-fibre eight days after tying the muscle; *d*, giant-cells, enclosing necrotic pieces of muscle, from a muscle-scar twenty-six days old; *e, f*, muscle-fibres ending in protoplasmic masses (muscle-buds), *e*, from a muscle-scar ten days old, *f*, from one twenty-one days old; *g*, dividing muscle-fibres from a muscle-scar forty-three days old. × 315.

versely striated muscle-substance passes without a sharp line of demarcation. There occurs, therefore, *at the same time with the multiplication of the nuclei an increase of the sarcoplasm of the muscle-fibres, and this becomes distinctly visible.*

The muscle-cells not connected with living contractile substance become changed into *large epithelioid cells with large nuclei* (*b*). Through continued division of the nucleus these cells become transformed into *multinuclear protoplasmic masses* (*d*); and a scar, consisting of proliferating connective tissue, of from eight to thirty days old, contains such giant-cells which often enclose the remains of old muscle-fibres (*d*) in large numbers.

The *new muscle-fibres develop for the chief part from the richly nucleated sarcoplasm*, which appears in the continuity and at the ends of the muscle-fibres, in connection with the formation of numerous large nuclèi, and which through its increase of size causes an increase in the thickness and length of the muscles, which has been designated *budding* by Neumann.

With the transformation of the sarcoplasm into muscle-fibrillæ there appears gradually a longitudinal and later a transverse striation, a sign that the organic structure of the plasma has completed its development in the way characteristic of muscle.

The greater part of the *proliferating muscle-cells which have no connection* with living muscle-fibres die; but it is to be noted that they persist for a long time, so that not infrequently there may be seen in muscle-scars from eight to forty days old great numbers of protoplasmic masses very rich in nuclei. Under certain circumstances these may form long, connected bands, or rows of separate pieces of protoplasm. There can be no doubt that a part of these cells under favorable conditions become transformed into transversely striated muscle-substance; and this takes place either by the formation of new independent muscle-fibres or by union with old muscle-fibres or muscle-buds. The disconnected new-formation of muscle from proliferating muscle-cells occurs particularly when the contractile substance is destroyed while the sarcolemma remains intact (as in typhoid fever). On the other hand, the formation of buds is observed especially at the ends of fibres which have been divided.

The buds springing from the ends or sides of muscle-fibres may cause a simple elongation of the muscle-fibre, frequently deviating from its original direction (*f*). Often there are seen fibres which have split into two or three parts (*g*), so that the old fibres branch as they pass into the muscle-scar. As far as we know, this splitting of the fibre occurs very early (*a*), before the proliferating muscle-nuclei have formed much sarcoplasm, so that the proliferation appears first in the split portions of the fibre. As a result of such splitting a muscle-scar may come to contain a greater number of muscle-fibres than were originally present in the affected area.

Hypertrophy of *transversely striated muscle* takes place through an enlargement of the individual muscle-fibres; the thin muscle-fibres in particular becoming increased in thickness (Morpurgo). The nuclei do not become increased in number. On the other hand, such an increase does take place in the case of a growth in length of the muscle; and is the result, most probably, of amitotic division (Morpurgo).

A **new-formation of heart-muscle** has not yet been positively demonstrated. After injuries of the heart, division figures appear in the muscle-cells, but after a few days these can no longer be demonstrated, and the wound heals through the formation of ordinary scar-tissue. Focal degenerations of the myocardium likewise heal by connective-tissue cicatrization.

A **new-formation of smooth muscle-fibres** as well as regeneration, occurs after traumatic or toxic and ischæmic degeneration. It occurs also in hypertrophic new-formations of muscle-tissue—for example, in tumors and is initiated by mitotic division of the nuclei of the muscle-cells, which is followed by division of the cells. According to the results of experimental work and also of observations upon the muscle-tissues of man, the reproduction of fibres after injuries and focal degenerations is but slight, ceasing after a short period. Thus, for example, defects in the muscularis of the stomach and intestines or of the bladder are, for the chief part, closed only by connective tissue.

Hypertrophy of smooth muscle-fibre is a phenomenon which, within certain limits, is of very frequent occurrence. In the pregnant uterus

the size of the muscle-cells may reach five to ten times the ordinary size. Of other organs the bladder most frequently shows a marked hypertrophy of smooth muscle.

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§ 86. **Regenerative new-formation of the nerve-elements of the central nervous system through the new-formation of ganglion-cells** most probably does not occur in man and mammals in post-embryonal life. According to the investigations of Stroebe, on the other hand, *divided nerve-fibrils* (in mammals) *may grow lengthwise to a certain extent*

through sprouting of the axis-cylinder; and this is true particularly of t fibres of the pyramidal tracts and the posterior roots, both of wh after being divided grow into the scar-tissue developing at the site of t wound, the former in a downward direction, the latter upward. A co plete restoration of nervous tissue does not take place, and a defect the spinal cord due to trauma is replaced essentially by connective t sue, in part also by neuroglia. According to investigations by Bo new axis-cylinders may be formed within the new-formed neuroglia the neighborhood of cerebral lesions, and medullary nerve-fibrils may produced by the outgrowth of old fibres.

Regenerative and **hypertrophic proliferations of neuroglia** are p nomena which occur frequently in diseased conditions of the cen nervous system, and either follow degenerative changes of the nerv elements, or in part also destruction of the neuroglia, or they m appear without s antecedents, in latter case arising part during the per of development.

The new-for tion is brought ab by mitotic division the nuclei and c bodies of the g cells, eventually of the ependyma-c

The newly for glia-cells produ later a great profu of delicate fibri processes (Fig. *a*), and, as in the mal tissues of the tral nervous syst there may be dis guished among t

FIG. 178.—Sclerotic tissue from the posterior columns of a case of multiple sclerosis (Müller's fluid, Mallory's method). *a*, Glia-cells with numerous processes, seen in longitudinal section; *b*, sclerotic tissue with transversely cut glia fibres. × 500.

cells which are known as *astrocytes* (Deiter's cells) two varieties, the called "*mossy cells*" (*Kurzstrahler*) and the so-called "*spider-cells*" (*L strahler*) with long, stiff, less-freely branching processes (*a*). processes of these cells form sometimes a loose, sometimes a dense work of fine fibrillæ (*a*, *b*) in which the cells, which have but little pr plasm, are embedded. After full development of the tissue a separa of the processes from the cell-bodies may take place. The thicker of the tissue caused by the proliferation is known as *sclerosis*.

Regenerative new-formation of the nerve-fibres of the periph nervous system is of very frequent occurrence and takes place in those cases in which through any influence the continuity of a ne fibre is entirely or partially interrupted. For its accomplishment, h ever, it is indeed necessary that the ganglion-cells whose processes f the nerve-fibres in question be preserved.

When a nerve has been severed, the axis-cylinders and medul sheaths, in the distal portion, undergo degeneration, the latter brea up into drop-like detritus, which later is dissolved. During the d tegration of the nerve-fibres the nuclei situated beneath the sheat

Schwann undergo mitotic division and form cells rich in protoplasm, which may take up into themselves the products of the destruction of the nerve-fibres.

Of the proximal portion of the nerve the peripheral extremity alone degenerates, as far as the next Ranvier's node, or the next one beyond.

The **regeneration of the nerves** begins a few days after the operation, in the proximal portion, about 0.4–2 cm. above the cut end.

The first change consists in a swelling of individual axis-cylinders in the peripheral parts of the nerve-bundle of the proximal end, which is later followed by a splitting-off of two to five or more new axis-cylinders. The new axis-cylinders arising in this way from the old ones grow in a longitudinal direction (Fig. 179, *a*, *b*) and form, within the sheath of Schwann, whole bundles (Figs. 179, *c*; 180, *e*) of newly formed nerve-fibres, which for the most part fill up the entire lumen of the old nerve-tubes, and indeed stretch it, and more rarely enclose remains of the old fibres (Fig. 180, *f*). Single fibres may even break through the old sheath of Schwann, and then either extend further in the endoneurium, or penetrate through the perineurium of the nerve-bundle into the epineurium.

FIG. 179.—Old and newly formed nerve-fibres from an amputation-stump, in longitudinal section (Müller's fluid, Weigert's stain). *a*, *b*, Old nerve-fibres, from which several young nerve-fibres have grown; *c*, neurilemma with young nerve-fibres. × 180.

In this way there are formed on the lower end of the proximal portion of the nerve a large number of new nerve-fibres, which in the beginning consist only of the newly formed axis-cylinders, but immediately surround themselves with a medullary sheath, which by reason of its irregular development gives to the nerve-fibres a varicose appearance (Fig. 179, *c*). Later the fibres acquire a neurilemma-sheath — that is, a connective-tissue covering which is probably formed from the nerve-corpuscles concerned in the proliferation.

When a nerve is entirely severed and there is no possibility of a union with the distal portion—as, for example, occurs in all amputations of the extremities—there is formed in the region of the cut end an embryonic tissue, springing from the connective tissue of the nerves, which later on becomes changed into connective tissue. In the beginning free from nerves this connective tissue becomes penetrated by young nerves growing out from the

FIG. 180.—Cross-section of a nerve-bundle of the median nerve just above a wound dividing the nerve, made four months previously (Müller's fluid, carmine). *a*, Perineurium; *b*, endoneurium; *c*, cross-section of a vessel; *d*, old unchanged nerve-fibre; *e*, bundle of newly formed nerve-fibres; *f*, newly formed nerves, with remains of old fibres inside the same sheath. × 200.

nerve-fibres of the nerve-stump, which, arranged in small bundle scattered, grow into the connective tissue and penetrate it in every di tion (Fig. 181). Not infrequently the growth of nerves is so exten that nodular or clubbed swellings (Fig. 181, *b*) arise on the ends of nerves. Such a swelling is known as an ***amputation-neuroma.***

When a nerve after division is again united, or if the division of nerve is only partial, the nerve-fibres growing out from the proximal after penetrating the connective ti formed in the site of the wound, ma part, or all, find their way into the ipheral portion of the nerve where, in mean time, the nerve-fibres have been stroyed. In this way the ***distal end again become neurotized***—that is, supp by new nerves. According to invest tions of Forssmann, the direction of newly growing fibres is governed chemotactic influences arising from disintegration-products of the old ne fibres.

According to the investigations Vanlair the growth of a regenera nerve is about 0.2–1 mm. daily, acc ing to the character of the tissue. portion of the new nerve-fibres may etrate into the old, empty sheath Schwann; others extend into the epin ium and perineurium, and in this si tion grow toward the periphery to end-organ. Single fibres may pass by end of the nerves, and grow toward periphery, either along the old nerve by an independent route. Many fib which leave the old route, are finally in the tissues. In the lower portion the intermediate substance (Vanlair) nerve-strands begin to collect bundles again, and with the forma of a perineurium about the latter, the generated nerve takes on more and m the structure of a normal nerve.

FIG. 181.- Amputation-neuroma of the sciatic nerve, in longitudinal section (amputation of nerve nine years previously) (Müller's fluid). *a*, Nerve; *b*, neuroma. × 8.

The above-described process of reg eration requires for its accomplishm weeks or even months, and sometimes is not complete after sev months.

The question of the **regeneration of the central nervous system** is still u discussion. It is generally accepted, as having been established beyond all doubt, in the cold-blooded animals, reptiles, and tailed amphibia, a regenerative new-fo gation of portions of the central nervous system can take place. In the case of w blooded animals, particularly in the mammals, the majority of experimental inv gations have failed to demonstrate a regenerative new-formation of ganglion- *Tedeschi*, *Vitzou* and others, claim to have observed, after injuries of various k both a new-formation of neuroglia and of ganglion-cells and nerve-fibres; but investigations carried out in my laboratory by *Tschistowitsch* seem to me to contr

these assertions. The results obtained by *Grunert* in experimental work with pigeons agree with the conclusions arrived at by *Tschistowitsch*.

Monti and *Fieschi* could demonstrate no evidences of regeneration in the ganglion-cells of the sympathetic after injuries. *Torelli* found only degenerative changes in the ganglion-cells of the intervertebral ganglion after injury of the same.

The **new-formation of peripheral nerve-fibres** has been made very frequently the subject of experimental research, and different observers have come to very different conclusions (see *Stroebe, l. c.*). The above-described mode of new-formation I regard as firmly established, in so far as its essentials are concerned, upon the ground of personal investigations. I have been unable to confirm the views of *Neumann, Dobbert, Daszkiewicz, Cattani, Weir Mitchell, Gluck, Beneke, von Büngner, Wieting,* and others, who hold that the new fibres in the distal portion of the severed nerve rise autochthonously from the nuclei of the sheath of Schwann, or from the old axis-cylinder, or from a protoplasmic mass formed by a chemical transformation of the medullary sheath and axis-cylinders (*Neumann-Dobbert*). The view held by *Bethe*, that the nerve-fibres arise without participation of the ganglion-cells in the fused ectodermatic cells whose remains later represent the cells of Schwann, appears to me to have been shown by von Kölliker to be incorrect. Likewise, the attempt made by *Neumann* and *Wieting* (*Marchand*) to bring into accord the established fact of the outgrowth of the axis-cylinders of the proximal portion into the scar uniting the severed ends, with the theory of the origin of new nerve-fibres from the nuclei of the sheath of Schwann, or from the remains of old fibres, or from both, by the assumption that the axis-cylinders growing from the proximal end convey a stimulus from the nerve-centres to the distal portion and thereby make possible the development of new fibres, I regard as unsuccessful, and hold to the above-given view. I am further of the opinion that the medullary sheath is not formed by the cells of the sheath of Schwann, but represents a product of the axis-cylinders; but further investigations as to this point are needed. According to *Nissl, Marinesco,* and others (see *Barbacci, l. c.*) there occurs, after the severing of a nerve, first a degeneration in the corresponding ganglion-cells with disintegration of the Nissl's bodies, and this may lead to the destruction of individual cells. Later, progressive changes with new-formation of chromatin take place, and may lead to hypertrophy of the cells (*Marinesco*); these changes reach their maximum in about ninety days, after which time there is a return to the normal condition.

The **regenerative new-formation of the tissues of the eye** has in recent years been repeatedly an object of research. According to *Wolff, Müller,* and *Kochs* the *lens* of tritons may regenerate, after removal, by means of a proliferation of the epithelium of the inner layer of the iris. According to *Röthig*, the same thing occurs in the trout. *Gonin* observed in rabbits, after the lens had been removed in such a manner that the capsule and some of the equatorial lenticular fibres and epithelium of the anterior wall were left behind, that there occurred a proliferation of this epithelium, leading to the union of the anterior and posterior walls through cells resembling connective-tissue cells. A new-formation of lenticular fibres from these cells does not take place. Remains of the lenticular fibres may form a rudimentary, useless lens, which in the case of young animals may become somewhat enlarged through the growth of the fibres. *Randolph* obtained somewhat better results in guinea-pigs. In the human eye similar formations are seen after removal of the lens, and are known under the name of "Krystallwulst" (*Baas*). According to *Franke, Krückmann,* and *Stoewer*, the sclera possesses but slight power of proliferation. Wounds of the same are healed chiefly through proliferation of the choroid and episcleral tissue.

According to *Baquis*, there occurs, in the injured *retina* of the rabbit, division of both ganglion and neuroepithelial cells. According to *Krückmann*, the pigment-epithelium is capable of extensive regeneration, but neuroepithelium, on the other hand, is not again formed.

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III. The Results of Transplantation and Implantation of Tissues and Organs.

§ 87. The local regeneration of tissue is, as mentioned in the last part, very often but slight, so that losses of tissue may be followed by permanent defects, and in place of the original structures there may appear only a cicatricial tissue of a lesser value. Consequently, from practical reasons, many attempts have been made, through **transplantation** and **implantation** of tissue, to aid and to improve the healing-process; and such attempts have in part been successful. At the same time they have also thrown light upon the individual life of the tissues and upon the behavior of the organism toward implanted living tissue.

The most successful results have been obtained in the *transplantation of tissues which remain connected with their nutrient vessels*, since the same, at the point of union between the transplanted portion and the underlying tissues upon which it is placed, grow together with the latter in essentially the same manner as do the edges of the wound in the case of a cut. This method is utilized most frequently in the case of plastic operations upon the surface of the body, but it finds application also in internal surgery. For example, wounds of the bladder, intestine, ureters, tubes, etc., may be easily closed through implantation of the omentum; and the surface presenting upon the lumen of the organ concerned becomes very quickly covered over by the neighboring epithelium, which extends over it from the edges, or is also transplanted from the opposite epithelial surface (Cornil, Carnot); while the omentum itself grows to the adjacent wound-surfaces, and thus through changes in its structure completely closes up the defect. Very often such an implantation of the omentum occurs spontaneously, as, for example, in the case of traumatic or ulcerative perforations of the intestine, stomach, gall-bladder, etc., and even large openings may be closed in this manner. As experimental investigations have shown, portions of intestine provided with blood-vessels may be implanted into other portions of the intestines, into the bladder (Enderle), stomach (Reerink), and can heal perfectly in these

locations with preservation of their own epithelium. Likewise, portions of bone or cartilage connected with the periosteum or perichondrium respectively, and with nutrient vessels, may be implanted into neighboring tissue.

Transplantations of tissues completely freed from their basement-structures have also been successfully performed, since cells loosened from their connection with the organism are able to preserve their vitality for a certain length of time. The cells of the epidermis are able to live for the longest time; when kept cool they may be preserved alive for several (two to nine) days (Wentscher claims to have been able to preserve epithelium alive for twenty-two days). Ciliated epithelium may also be preserved alive for several days and still show movements of the cilia. Next to the surface-epithelium in this respect stand the connective tissues, while other tissues quickly die, the cells of the brain and kidney most rapidly, dying within a few hours after an obstruction to the blood-supply. According to the investigations which have been made up to the present time the tissues of the skin, periosteum, inter-articular cartilages, muscle and cartilage easily preserve their vitality for two to three days. Morpurgo found cells of the periosteum to be capable of reproduction even after seven to eight days. The tissues of the vessels, tendons, and neurilemma appear to be somewhat more resistant. Exact statements with regard to this point cannot be made at present, since, on the one hand, the expiration of life does not take place suddenly, but gradually with the constant diminution of vital cells; and, on the other hand, the conditions under which the excised portions of tissue are preserved also influence the duration of life.

Transplantations of skin give the best results, and were first recommended by Reverdin and Thiersch for the healing over of broad, open wounds and have since been extensively used for this purpose. The material used consists of pieces of skin which may be taken either from the same individual or from another person. Ordinarily, strips of skin removed by means of a sharp knife are used, which include the tips of the papillæ and the upper layers of the corium. Epithelium in connection with a thicker layer of the corium may also be successfully transplanted, and in the case of injuries, large portions of the skin which have been completely torn off may be again joined by healing to the deeper tissues on the very same spot from which they had been removed.

The transplantation may be made either upon a fresh wound-surface or upon one already showing proliferation. The strips of skin are held firmly in place by means of moist bands of gauze. The pieces of skin become fastened to the surface of the wound by means of coagulated blood or lymph. In successful cases a firm union with the underlying tissue takes place within about eight days.

The nourishment of the transplanted pieces (Fig. 182, *d*) is obtained first from the tissue-fluids which exude from the underlying tissues. Later, there begins in the latter a vascular connective-tissue proliferation (*b*, *c*), and the transplanted portion becomes penetrated from below by new blood-vessels (*g*) accompanied by fibroblasts, so that it finally becomes interspersed with new blood-containing vessels and areas of granulation tissue. Under favorable conditions the old vessels may again become opened through the ingrowth of new vessels.

The behavior of the transplanted portion varies in individual cases, the number of cells living and proliferating changing with the condi-

tions. *A part of the cells of the transplanted portion is always lost,* and this is shown macroscopically in part by the repeated desquamation of the superficial layers of the epithelium (*f*). *Other cells, both epithelial and connective-tissue cells, proliferate and produce new tissue.*

The final outcome of a successful transplantation is the covering over of the area with transplanted epithelium and in part also by transplanted corium. Through the latter it is made possible that the cicatricial area comes to possess papillæ. To what extent in a given case the superficial layers of the cutis arise from the skin-graft or to what extent from the tissue upon which it is planted, cannot be determined. If the papillary

FIG. 182.—Skin-graft four and one-half days old (formalin, hæmatoxylin, picrofuchsin). *a*, Deep layer of the corium; *b*, proliferating granulation-tissue; *c*, boundary of proliferating zone; *d*, *e*, transplanted portion of skin; *f*, desquamation of the horny layer; *g*, vascular offshoots and granulation-tissue extending into the transplanted connective tissue. × 107.

bodies remain preserved, a portion of the tissue may be formed from immigrating fibroblasts. After a time the transplanted area comes to contain nerves which grow into it from the edges, and there is restored first the tactile sense (Stransky), later the sensibility of pain and temperature. New elastic tissue also develops, as in ordinary scars, from the ends of the old fibres.

Besides skin-transplantations, there have been attempted transplantations of almost all the tissues: periosteum, bone-marrow, bone, muscle, nerves, thyroid, pancreas, adrenals, mammary gland, mucous glands, ovary, testis, etc.; also of tissue-combinations, as, for example, a rat's tail from which the skin has been stripped. Embryonal tissue has also

been transplanted in a variety of ways. Finally the attempt has also been made to transplant tissues from one animal to another of a different species.

Such transplantations have been made upon open wounds, into the subcutaneous tissues, peritoneal cavity, glandular organs and lungs, either by direct operative procedures or by the introduction of the tissue into the blood-stream through the blood-vessels.

The results of all these experiments may be summed up as follows:

In all transplanted tissues there occurs first a degeneration, and a part of the tissue dies. After a certain time there usually results a *proliferation* of the remaining portion, which may lead to a new-formation of tissue. Connective-tissue cells form new connective tissue; periosteum and endosteum form bone or connective tissue; muscle-cells, new muscle; cartilage, new cartilage; surface epithelium, new epithelium (epithelial cysts). Of the glands the thyroid, mucous glands, and mammary glands may form new glandular tissue, while such a new-formation does not take place in the case of the kidney, liver, testis, and ovary. In the case of the liver only the epithelium of the bile-ducts proliferates. Only in the case of the transplantation of the ovary into the peritoneal cavity of the same animal can the ova ripen and pregnancy occur (Knauer, Ribbert, Gregorieff). The tissues of young individuals in general show a greater capacity for proliferation than those of old ones. In the case of the transplantation of complicated tissues, as, for example, the skinned tail of a rat, all the different tissues may produce new tissues and the whole piece grow.

Embryonal tissue can likewise grow after transplantation and become differentiated, and it is shown that firm cartilage in particular, which in later life shows but little power of proliferation, is longer preserved and shows further growth, while the delicate soft tissue-formations easily die.

After a certain time there occurs in almost all the transplanted tissues, as well as in the newly formed tissue, *a retrograde change*, and they are *finally destroyed through the ingrowth* of tissue from the neighborhood. The time at which this occurs varies with different tissues, and is dependent partly upon the character of the tissue, and partly upon the surrounding conditions. Implanted surface-epithelium can under certain conditions remain permanently, and give rise to *epithelial cysts*. Portions of thyroid, mammary gland, and pancreas are preserved for a long time. Cristiani found pieces of thyroid intact two years after implantation. The majority of the tissues, however, disappear within a few months. In glands which are not capable of proliferation the gland-cells die first. If all of the implanted piece is not destroyed it may become encapsulated.

Tissue of different species, when transplanted, does not grow, but is either *destroyed* or *encapsulated*, sometimes quickly, sometimes slowly.

According to the published observations, *the implantation of tissue does not lead to the formation of a permanent tissue* from the transplanted piece except in the case of the transplantation of skin. Nevertheless, such an implantation may, under especial conditions, have a transitory or permanent value. The implantation of thyroid or pancreas tissue may for a certain time check the harmful consequences of the loss of these glands. Through implantation of a tissue into a defect a temporary filling of the latter may be produced, and the neighboring tissues are thus permitted to proliferate for a longer time, and to form a greater amount of new tissue along the framework afforded by the implanted portion, and so finally to close up the defect completely. Bone (not connected with nutrient vessels) when implanted into a portion of the skeleton is destroyed, and

absorbed (equally so in either case, whether living bone or dead and macerated bone is implanted), and is replaced by new bone arising from the neighboring periosteum and endosteum. In this way there may be obtained a better healing of the bone-defect, and such implantations of bone or cartilage may also be made use of in the case of other tissues, for the stimulation of a more abundant production of tissue for the purpose of filling up tissue-defects.

The transplantation of nerves has never resulted in the new-formation of a nerve from the transplanted piece. The attraction which the products of disintegration of a nerve (Forssmann) exert upon the axis-cylinders growing into the wound may be utilized to direct the course of the growing nerves into certain channels.

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IV. Metaplasia.

§ 88. **Tissue metaplasia** is that process by which a *tissue already formed is changed into another closely related* without the intervention of a cellular embryonic or granulation-tissue stage. Tissue metaplasias play a very important rôle in the development of the individual connective-tissue formations, particularly in the formation of bone, cartilage, and marrow-tissue. Through proliferation of the periosteum or endosteum there is often first produced ordinary fibrillated connective tissue which later undergoes a transformation into osteoid tissue, bone, or cartilage. In the case of a *metaplasia of connective tissue into osteoid tissue* there occurs without further cell-proliferation a condensation of the ground-

substance (Fig. 183, *a*, *b*) which leads by a gradual transformation to the formation of an osseous ground-substance (*c*) staining red with carmine or eosin or fuchsin. Should there further occur a deposit of lime-salts (Fig. 184, *c*) true *bony trabeculæ* may be formed.

In the metaplasia of connective tissue into cartilage the ground-sub-

FIG. 183.—Periosteal formation of bone in a case of metastatic carcinoma of a rib. (Hæmatoxylin, picric acid, fuchsin.) *a*, Fibrillated connective tissue; *b*, connective tissue undergoing condensation; *c*, fully developed bone. × 300.

stance becomes thicker but at the same time more clear and stains less intensely (Fig. 185, *c*) than the connective tissue (*b*). The cells increase in size and come to lie in round spaces. Such changes may be observed in the periosteum and endosteum as the result of traumatic or infectious processes or in the new-formation of fibrous tissue associated with tumor formations (Figs. 183 and 185). In the healing of wounds in the tracheal cartilages which are first closed by scar-tissue developing from the perichondrium, cartilage may be developed later in the same manner (Fig. 186, *b*).

If normal or pathological *new-formed cartilage becomes penetrated by blood-vessels* the cartilage-cells after the dissolving of the ground-substance may form *reticular connective tissue* through the development of branched processes (Fig. 187, *b*, *c*), which through the enclosure of *marrow-cells* takes on the character of *marrow-tissue*, or through the taking up of fat by the cells may become changed into *adipose tissue*. If in the vascularization of the cartilage trabeculæ of cartilage remain, these may be transformed into *osteoid tissue* (Fig. 188, *f*) which when stained with hæmatoxylin and eosin

FIG. 184.—Formation of bone from connective tissue (alcohol, hæmatoxylin). Cross-section through a bone trabecula in process of formation; from an ossifying fibroma of the periosteum of the upper jaw. *a*, Connective tissue; *b*, thickened tissue, forming the groundwork of the new bone; *c*, deposits of lime-salts; *d*, connective-tissue cells; d_1, bone-cells. × 180.

takes an intense red stain, while the unchanged cartilage stains bl
Through the deposit of lime salts it may later be changed into bo
In chronic inflammation of the joints, *cartilage may be transformed i*

FIG. 185.—Periosteal formation of cartilage in metastatic carcinoma of a rib. (H
toxylin, picric acid, fuchsin.) *a*, Fibrillated connective tissue; *b*, connective tissue under
condensation; *c*, fully developed cartilage. × 300.

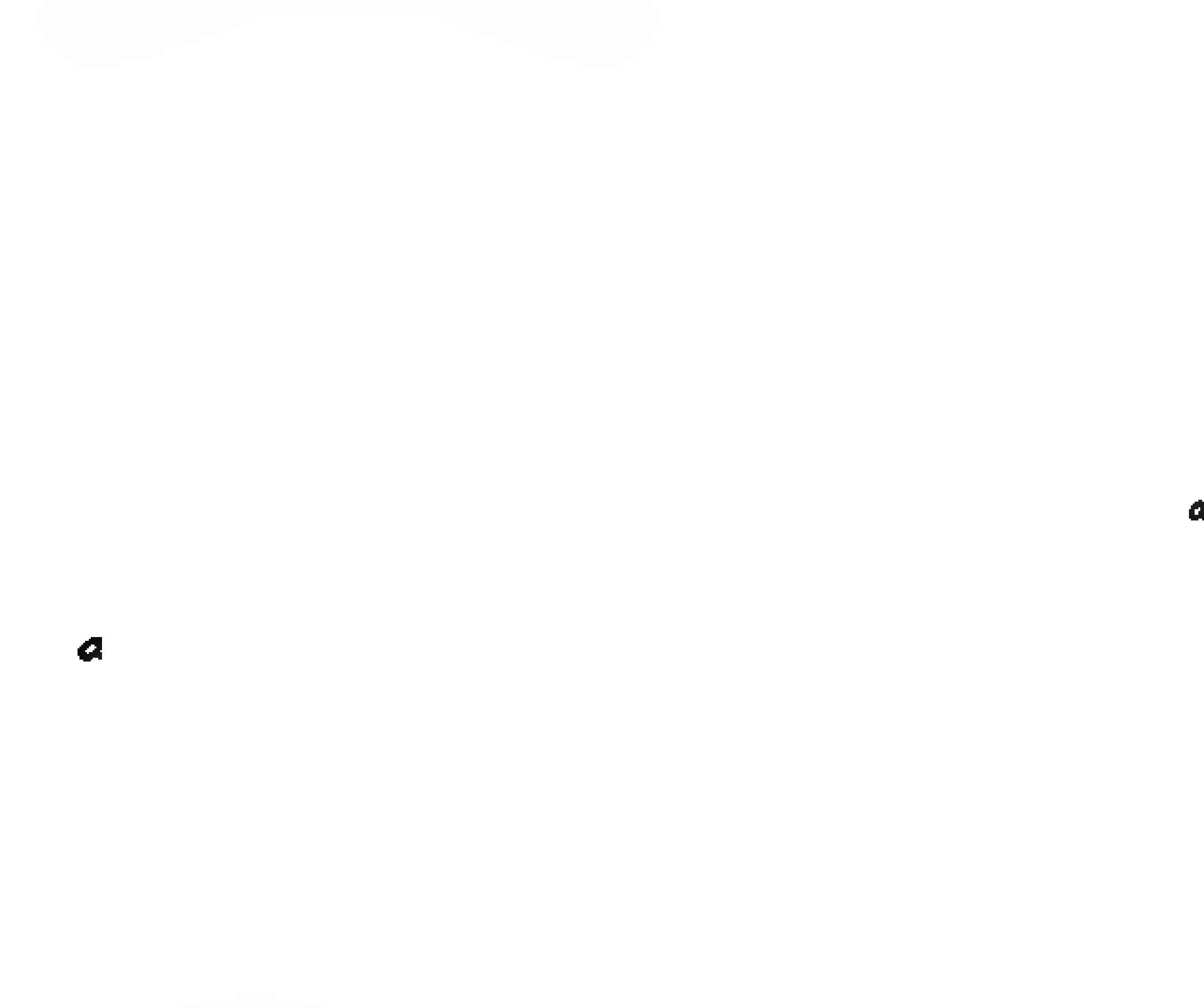

FIG. 186.—Healed tracheotomy wound in the cricoid cartilage, fifty-two days old (Fo
hæmatoxylin, and eosin.) *a*, Old cartilage; *b*, *b*, connective tissue arising from the perichon
undergoing metaplasia into cartilage. × 60.

ordinary fibrillated connective tissue, particularly when its free surface is covered with connective tissue.

The metaplastic processes thus described are connected with preced-

FIG. 157.—Metaplasia of cartilage into reticular tissue, in arthritis fungosa (alcohol, hæmatoxylin). *a*, Hyaline cartilage; *b*, tissue consisting of branched cells; *c*, cartilage-cells, set free by the liquefaction of the basement-substance of the cartilage, and becoming transformed into cells of mucous tissue. × 400.

FIG. 158.—Metaplasia of cartilage into osteoid tissue, in a callus fourteen days old (Müller's fluid, picric acid, hæmatoxylin, carmine). *a*, Hyaline cartilage; *b*, marrow-spaces; *c*, blood-vessel; *d*, cellular, *e*, fibrocellular marrow; *f*, osteoid tissue; *g*, osteoblasts; *h*, cartilage-cells freed through the disappearance of the ground-substance; *i*, proliferating cartilage-cells in opened capsule; *k*, proliferating cartilage-cells in closed capsule. × 200.

ing proliferations and may be associated further with appearances of proliferation. But there occur metaplasias, such as are described above, which have no connection with any proliferative change, or are only as-

sociated with it at a later period; thus myxomatous tissue may become changed into adipose tissue if the star-shaped tissue-cells become changed into round fat-cells through the taking up of fat, while the mucoid ground-substance disappears. Lymphadenoid tissue may, after the disappearance of the lymphoid elements, be changed into adipose tissue through the taking up of fat into the cells of the stroma. Through the disappearance of fat, adipose tissue may take on the appearance of mucoid tissue, and occasionally comes to contain mucin.

In the change of connective tissue into myxomatous tissue the fibrillæ vanish and there appears in their place a jelly-like mucus. If numerous lymphoid round cells collect in fibrillated connective tissue and there occurs at the same time a reticulation or a disappearance of the connective-tissue fibres, while the connective-tissue cells remain preserved and through the formation of processes unite themselves to form a reticular tissue, lymphadenoid tissue may be developed.

Epithelial metaplasia occurs most frequently in chronic inflamed mucous membranes, for example, uterus, urethra (gonorrhœa), nose (ozæna), and the trachea, cylindrical epithelium being transformed into pavement epithelium.

This change occurs in the following manner: after repeated loss of the original epithelium the regenerating epithelium changes its character. In mucous membranes possessing stratified pavement-epithelium the upper cell layers may show cornification, not only in places which normally possess pavement-epithelium, as, for example, the tongue and cheeks, but also in those possessing transitional epithelium (the urinary tract), or cylindrical epithelium (nose, ureters, and gall-bladder). In connection with this phenomenon should be mentioned the fact that epithelial tumors arising in mucous membranes possessing transitional or cylindrical epithelium may bear the character of squamous-celled epithelial tumors.

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CHAPTER VII.

Inflammation.

I. The Early Stages of Acute Inflammation.

§ 89. Under the designation **inflammation** are grouped those pathological phenomena which represent a **combination of different pathological processes,** consisting on the one hand of **tissue-degenerations** and **tissue-proliferations,** and on the other of **pathological exudations from the blood-vessels.** *Degenerations of tissue and pathological exudations initiate the process; with these tissue-proliferation is sooner or later associated,* the latter leading in the further course of the process to a *compensation for the disturbance*—that is, to *healing.* The *proliferation of tissue* may, therefore, be regarded as *regenerative,* but such new-formation of tissue may be in excess of that which is useful to the body. The tissue-degenerations and proliferative processes described in the previous chapters appear for the greater part as participating factors in inflammation; the *process acquiring its inflammatory character through the combination of tissue-degenerations and tissue-proliferations with pathological exudations.*

Deeper tissue-lesions—that is, *injury of tissues containing blood-vessels*—which in some way or other affect the vascular system, *will, therefore, constantly bear at some time during their course the character of an inflammation. The formation of scar tissue, the healing of transplanted tissues,* as briefly described in the last chapter, *always take place through processes essentially inflammatory in nature.*

Exudation in **acute inflammation** is constantly associated with a pronounced *hyperæmia,* which appears even before the beginning of the exudation, and hence ushers in the latter. As a result of the combination of hyperæmia and exudation the inflamed tissue becomes reddened and swollen. When situated on the surface of the body, where a cooling of the tissues takes place, the increased flow of warm blood from the deeper tissues causes a local increase of temperature. If the tissue affected contains sensory nerves, the sensation of pain will be produced as the result of the changed conditions in the inflamed area.

Redness, swelling, increased warmth, and **painfulness of the inflamed tissue** are phenomena which even in ancient times were regarded by physicians as the signs of inflammation; and **rubor, tumor, calor,** and **dolor** were designated by Celsus, at the beginning of our era, as the **cardinal symptoms of inflammation.** To these four was then added still a further symptom, **functio læsa, altered function** of the inflamed tissue.

The **causes of inflammation** may lie either in *mechanical, thermal, electrical,* or *chemical* influences, as well as in the *influence of parasites.* The common characteristic of all these injurious agencies is *the production, in the first place, of a local tissue-degeneration, which, when of a certain extent* and *intensity, is associated with disturbances of the circulation and of the vascular secretion.* The causes of inflammation are not specific; any

injurious agent may excite inflammation if on the one hand its action is sufficiently intense to cause certain disturbances of circulation in association with tissue-degenerations, but on the other hand not so intense as completely to destroy the tissue and stop the circulation.

The great majority of the causes of inflammation reach the human organism from the outside, but excitants of inflammation may be formed also within the body. In the first place bacteria which have penetrated into the tissues very often form within their protoplasm or from substances present in the body certain products which are capable of exciting inflammation. Moreover, substances that excite inflammation may arise within the organism without the aid of parasites; particularly as the result of the death of large masses of tissue from any cause, as, for example, as the result of anæmia, or when as the result of disturbances of metabolic processes (gout) products of metabolism are deposited in the tissues.

The causes of inflammation may act upon the tissues either from the portions of the body accessible from without, or from the lymph and the blood; and we may, therefore, distinguish **ectogenous, lymphogenous, and hæmatogenous inflammations.** Through the spread of an inflammation to neighboring tissues there arises an **inflammation by continuity**; as the result of the transportation through the lymph or blood stream of an agent causing inflammation, there are produced **metastatic inflammations.** If injurious substances are discharged through the excretory organs, **excretory inflammations** may arise.

When a local injury to tissues has reached such a degree as to produce the exudation characteristic of an inflammation, there is usually found in the first place a **congestive hyperæmia,** as a result of which the blood flows through the dilated blood-channels with increased velocity. After a short time there is a lessening of the speed of the circulation which leads finally to an abnormal **slowing of the blood-current.**

The first **disturbances of circulation,** which find expression in the congestive hyperæmia, may be due either to a stimulation or paralysis of the vasomotor system or to a direct action upon the vessel-walls, particularly upon the arterial walls, leading to a dilatation of the lumen. Although these disturbances very frequently precede the inflammatory exudation, they do not form an essential characteristic of inflammation, and occur very often without being followed by an inflammatory exudation. Further, they may be absent during the course of an inflammation. The circulatory disturbances characteristic of inflammation are shown only when the **slowing of the blood-current and the pathological exudation from the blood-vessels** set in. The slowing of the bloodstream in the dilated channels and the pathological exudation are dependent upon a *change in structure*, **an alteration of the vascular walls,** through which there results a lasting dilatation of the vessel and an adhesion of the blood to the vessel-wall, causing an *increase of friction-resistance* and an *increased permeability* of the vessel-wall. In the capillaries the persistent dilatation is in great part the result of *relaxation of the connective tissue surrounding the capillaries,* inasmuch as the thinness of the capillary walls makes this tissue bear the greater part of the blood-pressure resting upon them.

The **tissue-lesion** which leads to the phenomena of inflammatory disturbances of circulation and exudation usually affects all parts of the tissue, but under certain conditions may be limited to the vessel-wall, particularly in the case of a hæmatogenous inflammation, in which the

injurious agent acts from the blood. However, the tissue in the region adjoining the capillary walls must soon become involved in association. The tissue-changes brought about by the excitants of inflammation are sometimes only slight, and even on microscopical examination are either not recognizable at all or only with difficulty; at other times they are more severe, so that they may be easily recognized even on macroscopic examination. The latter is particularly the case when some time has elapsed after the action of the injurious agent. During the further course of the inflammatory process there are often added to the lesions produced directly by the causes of inflammation other tissue-changes, which are brought about by the inflammatory disturbances of circulation and the collection of exudate in the tissues.

If in any tissue the cause of inflammation has led to that alteration of the vessels which is the requisite antecedent of an inflammatory disturbance of the secretion of the vessels, i.e., the formation of an inflammatory exudate, and if as a result of this there is already evident a slowing of the blood-stream, the capillary circulation becomes irregular, and there occurs here and there either stagnation or a permanent or transitory stasis. Since in this event the white blood-corpuscles often remain clinging to the vessel-walls while the red blood-cells are carried on, there arises **in the capillaries** a more or less marked **increase of white blood-corpuscles** as compared to the red. **In the veins,** in which there can be distinguished in the normal circulation an axial red stream and a peripheral plasma-zone free from cells, a greater or less number of **leucocytes pass over into the peripheral plasma-zone,** when the slowing of the circulation has reached a certain degree. A still greater slowing of the current leads to the passing over of blood-plates and red blood-cells into the peripheral plasma-zone, and finally the difference between the axial-stream and the peripheral zone may be entirely lost.

When leucocytes pass over into the peripheral zone they either roll along in the same or cling to the wall of the vein, either to roll on again after a time or to remain permanently attached. If this occurrence leads to a marked accumulation of leucocytes along the vein-walls, the condition is known as the **marginal disposition of the white corpuscles** (Fig. 189, *d*).

Following the accumulation of the leucocytes in the capillaries and the marginal disposition in the veins there occurs later an *emigration of the leucocytes* (Fig. 189, *d, e*) from the vessels involved, and at the same time a *pouring-out of fluid from the vessels into the tissues.*

The **emigration of the white corpuscles** is an active process, which is accomplished through the amœboid movement of the cells, and to a certain extent occurs under normal conditions. The cause of the marked emigration seen in inflammations is doubtless a change in the vessel-walls, which favors the clinging of the cells to the walls and their passage through the latter. According to investigations by Arnold, Thoma, and others, the leucocytes pass out through the lines of cement-substance between the endothelial cells; and in the alteration of the vessel-wall due to inflammation localized defects occur in the wall as the result of the widening of these lines. The emigration is accomplished by the leucocytes first sending a process through the vessel-wall, the remainder of the cell-body then flowing after the process, until finally the entire cell-body is outside of the vessel. Arrived here the leucocytes first remain lying in the immediate neighborhood of the point of diapedesis, but often wander farther, the direction of the wandering being determined

partly by *mechanical stimuli*, partly by *chemotaxis*—that is, the repel
or attracting influences exerted by chemical substances present in s
tion in the tissue-juices. Possibly chemotactic influences someti
exert an action even upon the leucocytes in the capillaries or tho
the peripheral zone of the veins. The cells emigrating from the ve
are at first *polynuclear leucocytes*, but *lymphocytes* may very soon
company them. The polynuclear cells which occasionally alone
out, and in great numbers, are after their emigration known as
cells.

The **pouring-out of the fluid exudate,** whose composition al
differs more or less from that of the normal tissue-lymph, and whi
characterized by a *relatively high albumin-content*, is a process whi

FIG. 189.—Inflamed human mesentery (osmic-acid preparation). *a*, Normal trabecula; *b*,
epithelium (endothelium); *c*, small artery; *d*, vein with leucocytes arranged peripherally; *e*, white
cells, which have emigrated or are emigrating; *f*, desquamating endothelium; f_1, multinuclear ce
extravasated red blood-cells. × 180.

also to be referred to an *alteration of the vessel-wall*, in consequen
which the *secretory function of the latter suffers a disturbance.* It
place at the same time with the emigration of the leucocytes, but
begin before this event, and may occur also in cases in which the em
tion of the leucocytes (for example, as a result of a paralysis of the s
does not take place at all, or remains within very narrow limits.
composition of the exudate is dependent, in all cases, partly upon th
pecial property of the affected vessels, which always varies accordi
the tissue-formation to which the vessels belong, and partly upon
degree of vascular alteration; and it may be assumed that the albu
content is the higher the greater the damage to the vessel-walls. I
extravasated fluid contains fibrinogenic substances and fibrin-ferm
coagulation—that is, a **separation of fibrin**—takes place.

If the alteration of the vessels is of a very high degree, or if a
same time there is a marked stasis, **red blood-cells may also pass**
of the vessels (Fig. 189, *g*) along with the fluid, either by rhexis or

pedesis. According to Thoma and Engelmann the diapedesis occurs particularly in those places where leucocytes have previously passed through the vessel-wall, and the escape of red blood-cells may follow very quickly by the same route. Since the red blood-cells are not motile, their escape must be regarded as a passive process performed under the influence of the pressure within the capillaries.

The **escape of blood-plates** into the exudate may take place both in exudates rich in cells and those containing but few, but occurs particularly in exudates characterized by a rich content in fibrin and red blood-cells.

Tissue-proliferation—that is, the division of cells and nuclei—is first recognizable about eight hours after the action of the injurious agent; and in many cases appears much later. There are present, therefore, in case the inflammation does not arise in a tissue already in a state of proliferation, the characteristic appearances of inflammatory exudation, and with it also the tissue-degeneration, long before the proliferation begins.

The clinical significance of the term *inflammation* (*inflammatio, phlogosis*) has changed but little in the course of time, since the cardinal symptoms of inflammation set forth by Celsus, and accepted by Galen, are recognized as such at the present day. Nevertheless, the views regarding the differentiation of the essential from the unessential in the symptom-complex of inflammation and the accurate determination of the true nature of the process have differed greatly. A comparison of the expressions concerning these points made by the more modern writers (*Virchow, von Recklinghausen, Cohnheim, Ponfick, Samuel, Thoma, Neumann, Stricker, Heitzmann, Grawitz, Leber, Metschnikoff*, and others) shows that no single writer defines inflammation in the same way as any other, or interprets in exactly the same way any one of the individual phenomena of inflammation. *Ponfick* designates as the cause of inflammation the disturbance of equilibrium in the tissues, "but hesitates to designate retrogressive changes as an indispensable attribute of the inflammatory process, and doubts wholly that they should be regarded as the point of departure and the chief feature of the process." I am of the opinion that "a disturbance of the tissue-equilibrium" is nothing more than a degenerative change of tissue, and regard *Ponfick's* statement, though directed against my definition, as harmonizing with my views. Moreover, I once again emphasize the fact that the alteration of the vessels is a necessary requisite for exudation, and that this alteration is nothing else than a tissue-degeneration.

It was formerly believed that hyperæmia was the essential symptom of inflammation. *Rokitansky* held that every inflammation was characterized by a dilatation of the capillaries, slowing of the blood-stream, and by stasis, which was caused by a thickening of the blood through the effusion of serum and the adhesion of the red blood-cells to one another. *Henle, Stilling*, and *Rokitansky* attributed the dilatation of the vessels and the slowing of the circulation to a paralysis of the nerves of the vessels, the cause of which, according to *Henle* and *Rokitansky*, is an increased stimulation of the sensory nerves; while according to *Stilling*, the cause lies in a paralysis of the nerves due to the inflammatory irritant. *Eisenmann, Heine*, and *Brücke* sought to attribute the circulatory disturbances to a primary spasm of the vessels brought about by the irritation of sensory nerves, which produces behind the contracted portions of the vessels a slowing of the current, irregular circulation, and finally also stasis. *Vogel, Emmert, Paget*, and others, on the other hand, attributed the dilatation of the vessels and the stasis to an abnormal attraction of the blood by the tissues. Against these views it must be maintained that all the disturbances of circulation produced by contraction or dilatation of the vessels, indeed, introduce or accompany the inflammatory disturbances of circulation, i.e., those leading to exudation, and may exert a modifying influence upon the course of the inflammation, but do not form an essential part of the process, and may be entirely wanting, or may appear without the accompaniment of an inflammatory exudate.

Rokitansky sought to explain the pouring out of fluid from the vessels in inflammation by the assumption that with the dilatation of the vessels the walls of the latter became thinned and more permeable. *Vogel, C. Emmert*, and *Paget*, on the other hand, made this phenomenon also dependent upon an increased attraction between the blood and the tissue parenchyma or juices. *Virchow*, however (1854), believed that part of the exudate, and indeed that which collected in the tissue-spaces and is poured out upon the free surfaces of the body, to be the result of mechanical pressure in the vessels, i.e.,

pressed-out blood-serum; while a part, which is chiefly taken up by the "irritated" cells, is to be regarded as a product of an increased drawing of the blood-elements through the tissues, as a kind of nutritive educt. Of the cells collecting in the inflamed area, he believed that all originate from a proliferation of the tissue-cells occurring as the result of the action of the inflammatory irritant.

The recognition that the formation of the exudate is to be referred to an injury of the vessel-walls we owe chiefly to *Cohnheim*, whose investigations along various lines were completed by *Samuel*, *Arnold*, *Thoma*, *Binz*, and others. *Cohnheim* also showed that in inflammation the colorless corpuscles emigrate, and form an essential constituent of the inflammatory exudate.

Dutrochet ("Rech. anatomiques et physiologiques sur la structure interne des animaux et des végétaux et sur leur motilité," Paris, 1842, p. 214) and *Waller* (*Philosoph. Magaz.*, xxix., 1846, pp. 271, 398) had as early as the years 1842 and 1846 already described the escape of colorless corpuscles from the blood-vessels. These observations had, however, fallen completely into oblivion until *Cohnheim*, in 1867, rediscovered the phenomenon.

According to researches of *Schklarewsky* (*Pflüger's Arch.*, Bd. i.), the peripheral disposition of the leucocytes in the veins is purely a physical phenomenon. If fluids, in which are suspended finely powdered substances of different specific gravity, are made to flow through tubes, it will be found that at a certain degree of retardation of the current, the bodies of lighter specific gravity pass over into the peripheral zone, and at a more marked retardation the heavier bodies also enter this zone.

For the occurrence of the emigration of the white corpuscles, it is necessary, according to the researches of *Binz*, *Thoma*, and *Lavdowsky*, that they be capable of motion and of adhering to the vessel-wall. According to these observers, the emigration of the white blood-cells is not a purely passive, but is in part at least an active process. If the amœboid power of the white cells be lessened by means of irrigation of the mesentery with a 1.5-per-cent. solution of salt (*Thoma*), or if the vital energy of these cells be lowered by means of quinine or iodoform (*Binz*, *Appert*, *Kerner*), there results an inhibition of emigration. On the other hand, *Pekelharing* believes that quinine, oil of eucalyptus, and salicylic acid cause a contraction of the veins, lessen the permeability of their walls, and thereby hinder the passing-out of the white cells. This view is rejected, however, by *Disselhorst*, who observed a dilatation of the veins after irrigation of the tissues with quinine, carbolic acid, salicylic acid, and mercuric chloride. As there occurs in this case a retardation of the current after a transitory acceleration, without an emigration of the leucocytes collected in the peripheral zone; and as, on the other hand, leucocytes from blood-vessels that have been irrigated for an hour with quinine still retain complete vitality (*Eberth*), *Disselhorst* is of the opinion that the drugs mentioned so change the inflamed vessel-wall that an adhesion of the leucocytes rolling along the wall either cannot occur at all or only with difficulty.

It is very probable that a lesion of the vessel-wall is not absolutely necessary for the emigration of leucocytes (*Thoma*). Since vasomotor disturbances of the circulation can produce migration (*von Recklinghausen*, *Thoma*), it is probable that all of the conditions necessary for this process are furnished by a slowing of the blood-stream with peripheral disposition of the colorless corpuscles and the ability of the leucocytes to perform amœboid movements and to adhere to the vessel-walls. It is possible that differences in the water-content of the tissues (*Thoma*) also exert some influence, since an increased amount of water causes increased amœboid movement. It is also possible that the presence, in the tissue-fluids, of substances having active chemotactic properties may cause emigration of those leucocytes in the peripheral zone which are adherent to the vessel-wall.

According to the investigations of *Arnold*, *Thoma*, and *Engelmann*, there is present between the edges of the endothelial cells a soft cement-substance which suffers a change in the circulatory disturbance associated with cell-migration. This change may sometimes, but not always (*Löwit*), be recognized, on histological examination, in the form of numerous circumscribed widenings of these intercellular areas (*Engelmann*). If leucocytes pass through these places in great numbers the cement-substance becomes still more permeable, and may then permit also lymphocytes and red cells to pass through in rapid succession (*Thoma*).

Wandering cells are found normally in many tissues (*von Recklinghausen*), and wander from these partly into the lymph-vessels (*Hering*, *Thoma*), and under certain conditions also into the blood-vessels (*Bubnoff*, *Schulin*, *Ranvier*, *Senftleben*), or onto the surface of the mucous membranes, where they penetrate between the epithelial cells. They are found constantly in large numbers about the nodes of lymphadenoid tissue in the mucous membranes, and wander from these through the epithelium onto the surface. According to observations by *Kunkel* and *Siebel*, small numbers also reach the free surface of the alveoli of the lungs.

The inflammatory disturbances of circulation and the formation of exudates may be most easily followed in the transparent membranes of cold-blooded animals, particularly in the mesentery; or the extended tongue or the spread-out web of the frog. In the frog's mesentery, which has been spread out on a suitable glass plate, circulatory disturbances and inflammation develop simply through exposure to the air and the resulting evaporation; in the case of the tongue and web, it is necessary to cauterize in order to produce an inflammation. By the employment of suitable apparatus the circulation of the blood and the formation of the inflammatory exudate may also be observed under the microscope in the thin membranes of mammals (mesentery of rabbit, wing-membrane of bat), and observations thus made harmonize wholly with those made upon the frog.

The modern conception of inflammation is that it is a *pathological complex essentially adaptive, protective, and reparative, called into action by a primary tissue-lesion.* For a presentation of this view see *Warthin*, Chapter on Inflammation, "American Practice of Surgery," Vol. I.

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See also §§ 90–98.

§ 90. The *cellular and fluid exudates* secreted by the vessels collect first in the immediate neighborhood of the vessels (Fig. 189), but soon spread out in the vicinity, mass themselves in the *lymph-spaces* of the tissue, and thus form a **tissue-infiltrate** (Figs. 190, *e;* 191, *b;* 194, *p*). When the exudate is very abundant it may spread into and infiltrate the neighboring sound tissue that has not been injured by the inflammatory irritant. This **infiltration** may be so marked that new disturbances of circulation and nutrition may be produced, and the *area of tissue-degeneration and inflammatory exudation becomes increased in extent.*

The *exudate* present in a tissue *may be in part absorbed by the tissue-elements,* so that they become swollen, separated from their surroundings

(Fig. 190, *c*, *d*), and not rarely contain *drops of fluid* (*d*) which are commonly designated *vacuoles*. There often occurs also a complete **dissolu-**

FIG. 190.—Recent purulent meningitis (Müller's fluid, hæmatoxylin). *a*, Arachnoid; *b*, subarachnoideal tissue; *c*, *d*, desquamated endothelium; *e*, pus-corpuscles. × 300.

tion of the tissue-elements in the exudate, especially of the connective-tissue cells (Fig. 192, *d*, *f*), and not infrequently, also, of the intercellular

FIG. 191.—Hæmatogenous staphylococcus myositis (alcohol, hæmatoxylin-eosin). *a*, Transversely cut muscle-bundles; *b*, purulent, *c*, seropurulent, partly coagulated exudate. × 45.

substance. In this way both brain and muscle tissue, as well as ordinary connective tissue, may become completely liquefied in the course of inflammation, but this happens only when the tissue has been killed as a result of the tissue injury.

If dead cells become saturated with lymph containing fibrinogen, and

if fibrin-ferment is formed, the liquefaction of the infiltrated tissue may be preceded by a **coagulation**, whereby the cells become changed partly into homogeneous masses without nuclei, and partly into granular or fibrillar masses.

FIG. 192.—Section through the border of a blister caused by a burn (alcohol, carmine). *a*, H[...] layer; *b*, rete Malpighii; *c*, normal papillæ; *d*, swollen cells, some of whose nuclei are still visible th[...] pale, while others have been destroyed; *e*, interpapillary epithelial cells, the deeper ones intact, those o[...] upper layers are drawn out longitudinally and in part are swollen and have lost their nuclei; *f*, [...] liquefaction of the cells; *g*, interpapillary cells, without nuclei, swollen and raised from the cutis; *h*, [...] degeneration of interpapillary cells which have been raised from the cutis; *k*, coagulated exudate (f[...] lying beneath the uplifted epithelium; *i*, flattened papillæ infiltrated with cells. × 150.

If the exudate within an organ—for example, in a muscle—lies chi[...] in the supporting tissue, while the specific parenchyma appears but li[...]

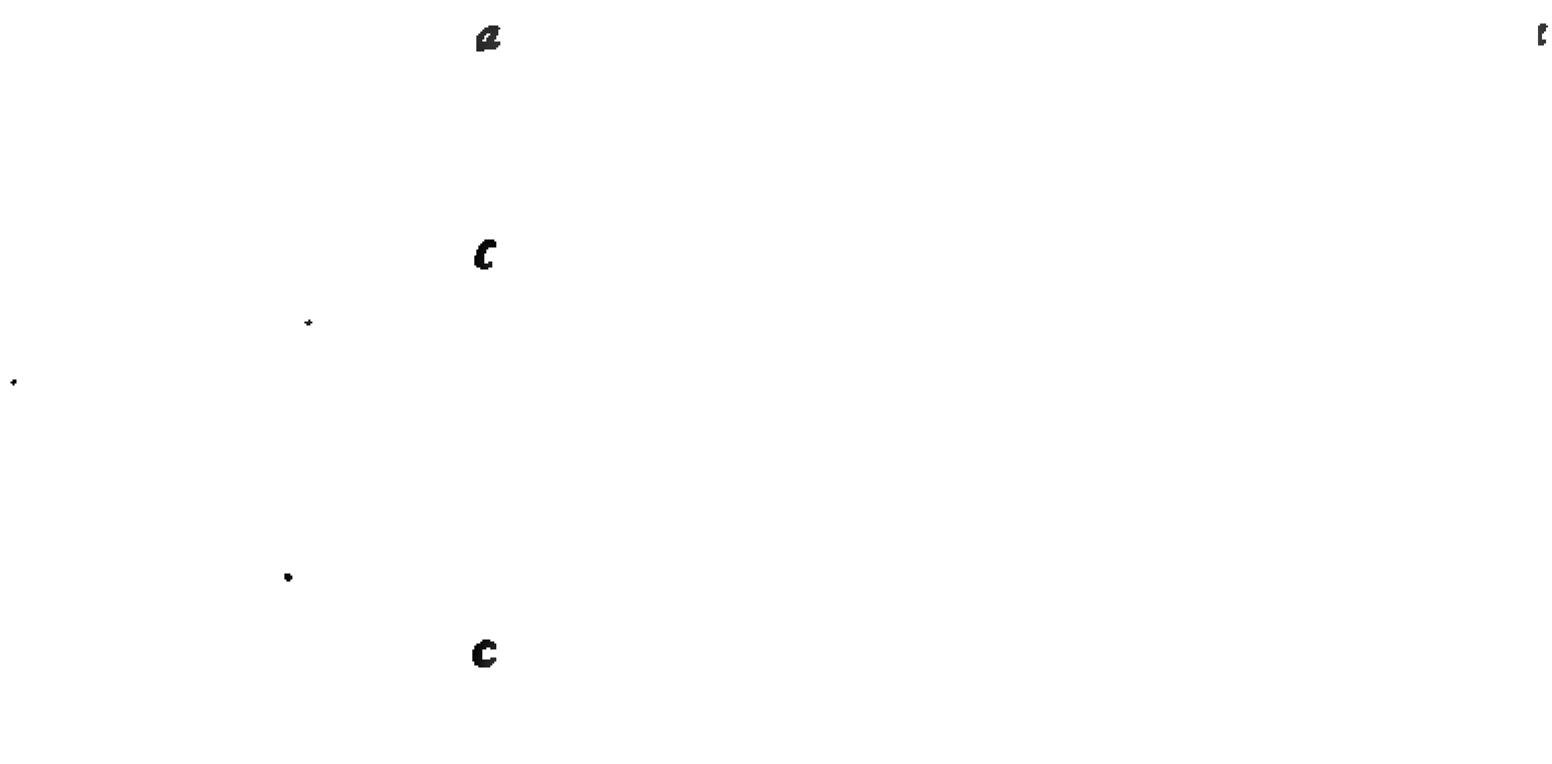

FIG. 193.—Parenchymatous hepatitis (Flemming's solution, safranin). *a*, Liver-capsule; *b*, liver-rods [...] ing fatty degeneration; *c*, liver-cells showing total degeneration. × 300.

changed, the inflammation is designated as an **interstitial inflamma**[...] (Fig. 191, *b*). If, on the other hand, the degeneration of the spe[...]

tissue—i.e., the epithelium of the kidney tubules, the liver-cells (Fig. 193, *b*, *c*), or the contractile substance of the muscles—is the most prominent feature of the process, the condition is called a **parenchymatous inflammation.**

When the seat of an inflammation is on the surface of an organ, it is termed a **superficial inflammation** (Fig. 194). If the exudate gains free access to the surface and flows from the same mixed with desquamated portions of the tissue (Fig. 194, *d*, *e*, *f*, f_1, *g*, *h*), the inflammation is called a catarrh. If the pouring out of a fluid exudate on the surface of the skin or mucous membrane is hindered by a coherent horny epithelial layer (Fig. 192, *a*), and if beneath this covering there are formed circumscribed collections of fluid, in which the deeper and softer layers of

FIG. 194.—Mucous catarrh of a bronchus (Müller's fluid, aniline-brown). *a*, Ciliated epithelium: a_1, deeper cell-layers; *b*, goblet-cells; *c*, cells showing marked mucous degeneration; c_1, mucoid cells with mucoid nuclei; *d*, desquamated mucoid cells; *e*, desquamated ciliated cells; *f*, layers of drops of mucus; f_1, layer consisting of thready mucus and pus-corpuscles; *g*, duct of mucous gland filled with mucus and cells; *h*, desquamated epithelium of the excretory duct; *i*, intact epithelium of the duct; *k*, swollen hyaline basement-membrane; *l*, connective tissue of the mucosa, infiltrated with cells in part; *m*, dilated blood-vessels; *n*, mucous gland filled with mucus; n_1, lobule of mucous gland without mucus; *o*, wandering cells in epithelium; *p*, cellular infiltration of the connective tissue of the mucous glands. × 110.

the epithelium dissolve (Fig. 192, *d*, *f*, *g*, *h*), the lesions thus produced are called **vesicles** and **blisters.** When the exudate from serous surfaces collects in the body cavities, there are formed in the latter **inflammatory effusions,** which not rarely reach a very large size, distend the affected cavity, and compress the organs contained within it.

It is customary to express the occurrence of an inflammation of an organ by adding the termination "*itis*" to the Greek name of the organ. Thus, for example, are formed the terms endocarditis, myocarditis, pericarditis, pleuritis, peritonitis, encephalitis, pharyngitis, keratitis, orchitis, oöphoritis, colpitis, metritis, hepatitis, nephritis, amygdalitis, glossitis, and gastritis. The ending "itis" is also sometimes affixed to the Latin names, as, for example, conjunctivitis, tonsillitis, and vaginitis. To denote an inflammation of the serous covering of an organ or of the

tissues immediately about it the prefixes "peri" and "para" are placed before the Greek names with the termination "itis." Thus, for example, are formed the words perimetritis, parametritis, periproctitis, perityphlitis, paranephritis, and perihepatitis.

For certain forms of inflammation especial names are used, as, for example, inflammation of the lungs is called pneumonia, and inflammation of the palate and tonsils, angina.

Since *Cohnheim* taught that the migration of leucocytes *en masse* is an important feature of inflammation and serves as a source for the cells in the exudate, the question of the origin of the cells present in the exudate of acute inflammations has been many times the subject of discussion. While some have regarded all the cells in the exudate as extravasated leucocytes, others have held that the leucocytes arising from the blood-stream form only an unessential element, and that the main part of the cells in the exudate have arisen on the spot from the tissue "irritated" by the cause of the inflammation.

Stricker held the opinion that the swelling and hardening of the tissues in inflammation are not caused by the collection of exudate, but by the swelling of the cell-reticulum which was thought to traverse the tissues; and that these changes represent a phenomenon of growth of the cells and their processes which is characterized by swelling. The cellular exudate—that is, pus—he accounts for partly through the segmentation and division of the cell-reticulum swollen by the inflammation, and partly through a transformation of connective-tissue fibrillæ into pus-corpuscles. *Heitzmann* regarded the inflammatory tissue-changes as a reversion of the tissue to the embryonal condition, and believed that the living material is not contained in the cells alone, but infiltrates the entire ground-substance, and increases, in the progress of an inflammation, with the liquefaction of the ground-substance. Connective-tissue cartilage and bone become resolved during inflammation into those elements from which they are formed—i.e., into cells—which then immediately reproduce their kind. *Grawitz* believes that both the cellular infiltrate and pus are formed without any participation of the leucocytes worth mentioning. Everywhere in the tissue, according to his view, there lie concealed in great numbers cells, which he designates slumber-cells, and which are not affected by our nuclear stains and therefore not recognizable (according to him, only from five to ten per cent. of the tissue-cells are known to us); these cells awake in inflammation, and again come into sight—that is, increase in size, stain with nuclear stains, and therefore again become recognizable.

According to the results of an unprejudiced and careful examination of inflamed tissues, there can be no doubt that the description of the origin of the inflammatory infiltrate given by *Stricker*, *Heitzmann*, *Grawitz*, and their pupils, does not correspond to the conditions as they actually exist. The cells which lie in recently inflamed tissue consist in part of leucocytes which have wandered from the vessels and in part of tissue-cells which are more or less degenerated, and are often separated from the underlying tissues. Later, to these there are added newly formed cells which have arisen through the division of preëxisting tissue-cells.

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See also §§ 89, 91, and 92.

§ 91. Both the *local tissue-degeneration* and the *exudation* may *vary greatly* in different cases, and there may be distinguished accordingly different **forms of inflammation.**

If the exudate consists essentially of fluid, while the cellular constituents are insignificant, it is called a **serous exudate.** When contained within a tissue—for example, within the skin and subcutaneous tissue, or in the lungs—there results an **inflammatory œdema.** The escape of the fluid on the free surface of a mucous or serous membrane gives the picture of a **serous catarrh**; circumscribed collections of fluid beneath the

FIG. 195.—Purulent desquamative catarrh of the trachea in measles (alcohol, hæmatoxylin, eosin). *a*, Layer of pus-corpuscles and desquamated epithelium; *b*, intact deepest layer of epithelium; *c*, basement-membrane; *d*, hyperæmic and infiltrated connective tissue of the mucosa; *e*, infiltrated submucosa with mucous glands. × 100.

horny layer of the epidermis with the liquefaction of the soft layers of epithelium lead to the formation of **vesicles** and **blisters** with clear contents (Fig. 192, *d*, *f*).

When the exudation of fluid on the surface of a mucous membrane is associated with a marked mucoid degeneration of the superficial epithelium (Fig. 194, *b*, *c*, c_1), and of the mucous glands (*n*), there arises a

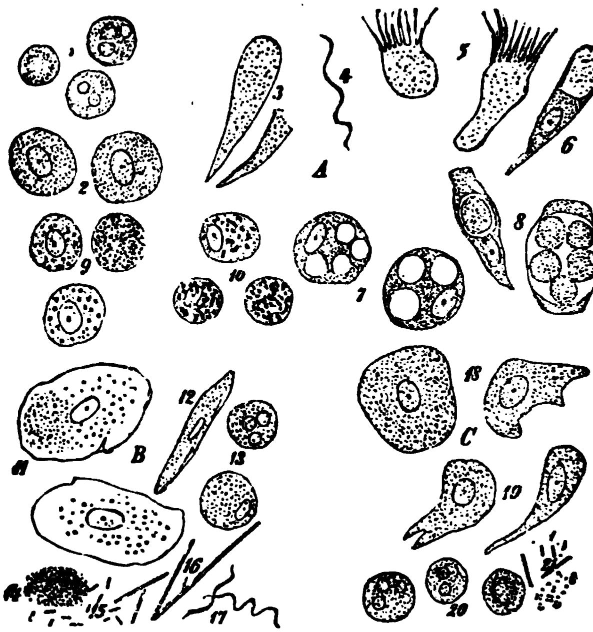

FIG. 196.—Catarrhal secretion of different mucous membranes. *A*, Secretion from mucous membranes with columnar cells; *B*, from the mouth; *C*, from the bladder. 1, Round cells (pus-cells); 2, large round cells with bright nuclei, from the nose; 3, mucoid columnar cells from the nose; 4, spirillum from the nose; 5, mucoid cells with cilia, from the nose; 6, goblet-cells from the trachea; 7, round-cells with spherules of mucus from the nose; 8, epithelial cells containing pus-corpuscles, from the nose; 9, fatty cells from a chronic catarrh of the pharynx and larynx; 10, cells containing carbon pigment, from the sputum; 11 and 12, squamous epithelium from the mouth; 13, mucoid pus-corpuscles; 14, micrococci; 15, bacteria; 16, *leptothrix buccalis*; 17, *spirochæte denticola*; 18, superficial, 19, middle layer of bladder epithelium; 20, pus-corpuscles; 21, *schizomycetes*. × 400.

mucous catarrh (*d*, *f*, f_1, *g*). If a marked desquamation of the epithelium, with or without a mucoid change, occurs (Fig. 195, *a*), the condition is termed a **desquamative catarrh**; and such a process may occur not only on mucous membranes, but also in the respiratory parenchyma of the lungs, on serous surfaces (Fig. 189, *f*, f_1), in the kidney-tubules, etc. If many pus-corpuscles are present in the exudate it may be spoken of as a **desquamative purulent** (Fig. 195, *a*), or finally as a pure **purulent catarrh,** in which condition the exudate becomes white or yellowish-white, milky or creamy.

The form and character of the cells of a catarrhal secretion vary with the location and the variety of catarrh (Fig. 196). Bacteria are often present in the cells of the exudate (Fig. 196, *4*, *14*, *15*, *16*, *17*, *21*).

If in a fluid exudate there occurs a deposition of fibrin or coagulation, there are formed **fibrinous** and **serofibrinous exudates,** which are often designated as **croupous.** These occur chiefly upon the surface of serous and mucous membranes, and in the lungs; but masses of fibrin

may be formed in tissues infiltrated with exudate, as well as in lymph-vessels.

On the mucous membranes the fibrinous exudates form whitish patches and coherent membranes, which sometimes lie upon them only loosely, but at other times are firmly attached to the underlying surface. In the serous cavities the fibrinous coagula float in the form of flakes in the fluid portion of the exudate, or form a firmly attached deposit upon the surface of the membranes. Such deposits consist at times only of thin, attached films or granules which give to the wiped-off surface a cloudy, lustreless, rough, or granular appearance; at other times of larger yellowish or yellowish-red, firm membranes, which often give to the surface a felted or villous appearance (cor villosum). In the lung, croupous inflammation leads to a filling of the alveoli with a coagulated mass, in consequence of which the lung acquires a firm consistence.

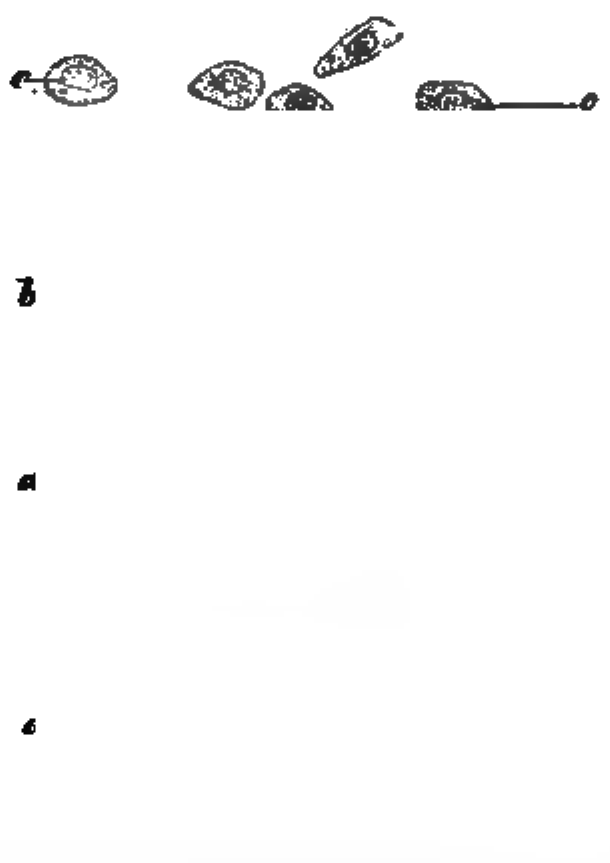

FIG. 197.—Acute hæmorrhagic fibrinous inflammation of the trachea, caused by vapor of ammonia (Müller's fluid, hæmatoxylin, eosin). *a*, Superficial layer of the connective tissue of the mucosa, with greatly dilated blood-vessels and extravasated red blood-cells; *b*, deep layer of epithelium raised up *in toto*; *c*, desquamated epithelial cells; *d*, hæmorrhagic fibrinous exudate with radiating, crystal-like masses of fibrin, in part proceeding from small, colorless spherules. × 300.

On *mucous surfaces* the formation of croupous membranes takes place when the epithelium is already desquamated and the connective tissue, at least in part, is exposed; but tissues covered with epithelium may also become the seat of fibrinous deposits extending from denuded areas. The desquamation of the epithelium, in such a case, may follow gradually, or at other times more rapidly through the lifting up of whole layers of epithelium (Fig. 197, *b*), which are either well preserved or already degenerated or necrotic, and infiltrated with exudate (Fig. 199, *a*).

The exudation of fibrin may begin underneath the raised-up epithelium with the formation of fine needle-like forms resembling crystals (Fig. 197, *d*), which are arranged radially about a centre, in which at times there lies a small body, probably a product of the disintegration of a red corpuscle, or a blood-plate. Very soon there form thicker or thinner threads (Figs.

FIG. 198.—Croupous membrane from the trachea. *a*, Section through membrane; *b*, uppermost layer of the mucosa infiltrated with pus-corpuscles (*d*); *c*, fibrin threads and granules; *d*, pus-corpuscles. × 250.

198, *c*; 199, *b*, *c*) which enclose a larger or smaller number of leuco and red blood-cells. The arrangement of the threads is usually re lar, but the thickness of the network and the size of the meshes greatly. When there is unequal development of the fibrin threads strands, the principal strands sometimes lie parallel with the su of the mucous membrane (Fig. 198, *c*), sometimes perpendicular

FIG. 199.—Section from an inflamed uvula covered with a stratified fibrinous membrane, fro of diphtheritic croup of the pharyngeal organs (Müller's fluid, hæmatoxylin, eosin). *a*, Surface coagulum, consisting of epithelial plates and fibrin and containing numerous colonies of cocci; *b*. layer of coagulum, consisting of fine-meshed fibrin network enclosing leucocytes; *c*, third layer of co lying upon the connective tissue, and consisting of a wide-meshed reticulum of fibrin enclosing leu *d*, connective tissue infiltrated with cells; *e*, infiltrated boundary layer of the connective tissue of the membrane; *f*, heaps of red blood-cells; *g*, widely dilated blood-vessels; *h*, dilated lymph-vessels fil fluid, fibrin, and leucocytes; *i*, duct of a mucous gland distended with secretion; *k*, transverse sect gland; *l*, fibrin reticulum in the superficial layer of connective tissue. × 45.

(Fig. 199, *c*). Thick fibrinous membranes frequently show a di stratification (Fig. 199, *a*, *b*, *c*), indicating that their formation ha curred in successive batches pushed up from below.

When a mucous membrane becomes the seat of a deposition of fi the underlying connective tissue is always more or less hyperæmic 199, *g*), œdematous and swollen, infiltrated with leucocytes (Figs. *d*, *e*; 200, *e*), and usually contains here and there also thready precipitates (Figs. 199, *l*; 200, *f*). Very often the tendency t

FIG. 200.—Croupous tracheitis. Section through the connective tissue of the mucosa (carmine and fibrin-stain). *a*, *b*, *c*, *d*, Blood-vessels with fibrin precipitates; *e*, oedematously swollen connective tissue with leucocytes; *f*, connective tissue with fibrin-threads. × 500.

FIG. 201.—Traumatic fibrinopurulent peritonitis (alcohol, Van Gieson's). *a*, Peritoneum of the abdominal wall; *b*, serosa of a knuckle of intestine which had been sutured to the wall; *c*, epithelium remaining intact; *d*, *e*, fibrin-deposit. × 200.

FIG. 202.—Fibrinous pleuritis (alcohol, Van Gieson's). *a*, Connective tissue; *b*, desquamated epithelium; *c*, thick, homogeneous, *d*, granular layer of fibrin with leucocytes. × 100.

precipitation of fibrin is manifested also within the blood-vessels (F
200), inasmuch as these contain at times tangled threads and rods
fibrin (Fig. 200, *b*), at other times fibrin-needles grouped in stel
forms or in clusters (*a*, *c*, *d*), which often proceed from degenera
endothelial cells or leucocytes, or from blood-plates, or radiate from portions of the vessel-wall where the endothelium is lost. Likewise, fibrin-threads may be also found in the dilated lymph-vessels, in association with fluid and cellular exudate (Fig. 199, *h*).

On the *serous membranes* the deposits of fibrin appear partly in granular (Fig. 202, *d*) and thready (Fig. 201, *d*, *e*), or in thick, homogeneous masses (Fig. 202, *c*), or even in the form of ribbon-like bands. Here also the epithelium is exfoliated at the point of deposition (Figs. 201, *d*, *e*; 202, *c*), but may be preserved in patches and covered over with fibrin (Fig. 201, *c*). The connective tissue of serous membranes in croupous inflammation is sometimes more, sometimes less infiltrated, and may contain leucocytes and fibrin, both in the congested vessels themselves (Fig. 200, *g*) and in the connective-tissue spaces (Figs. 200, *e*, *f*; 203, *c*). More marked exudations of fibrin upon the surface of serous membranes may produce thick, felted deposits, the formed elements of which consist of thready fibrin and pus corpuscles (Fig. 203, *d*, *e*), as well as micro-organisms (*b*). An abundance of pus-corpuscles gives to the exudate a *fibrinopurulent* character, the yellowish deposits becoming more whitish in color.

Fibrinous exudates in the

Fig. 203.—Fibrinopurulent diplococcus pleuritis in a three
old child (formalin, fibrin-stain). *a*, Inflamed pleura; *b*,
cocci; *c*, fibrin; *d*, *e*, fibrinopurulent exudate. × 300.

lungs are characterized by the formation of a more or less close network of fibrin-threads (Fig. 204, *b*), in whose meshes and in the immediate neighborhood of which lie leucocytes and usually also red blood-cells (*c*), mingled with desquamated epithelium. In the first stages there are also found occasionally globular, wreath-shaped precipitates of fibrin joined together in rows. Fibrin-threads may develop also in and upon dead epithelium (Hauser).

In the *kidneys* deposits of fibrin may occur in the form of fine threads or hyaline masses in the urinary tubules and glomerular capsules. In the *lymph-glands* fibrin-threads are formed particularly in the lymph-channels.

Hæmorrhagic exudate—that is, an exudate containing large numbers of red cells—occurs especially in connection with the exudation of fibrin. The exudate of croupous pneumonia constantly contains a larger or smaller number of red blood-cells (Fig. 204, *c*), and likewise in fibrinous pericarditis and pleuritis great numbers of red blood-cells not infrequently escape from the vessels. Hæmorrhagic inflammations occur not infrequently in the central nervous system, in lymph-glands, in the skin and kidneys. In the last case the blood escapes from the glomerular vessels.

FIG. 204.—Croupous pneumonia. Red hepatization of the lung (alcohol, carmine, fibrin-stain). *a*, infiltrated alveolar septa; *b*, fibrinous exudate; *c*, red blood-cells. × 200.

The serous, fibrinous, and serofibrinous inflammations are caused by thermal and chemical influences, as well as by bacteria; but are most frequently the result of infection, particularly of infection with the *Diplococcus pneumoniæ* (Fig. 204, *b*) and the *Bacillus diphtheriæ*. The former causes particularly croupous inflammations of the lungs and pleura, the latter gives rise to fibrinous inflammations of the throat, palate, and respiratory passages.

Neumann holds the opinion that in *recent* fibrinous inflammations of the serous membranes the hyaline bands and lumps on the surface of the membrane are not exudative fibrin, but represent layers of connective tissue that have undergone a fibrinoid degeneration. I cannot subscribe to this view, but agree rather with the majority of writers who have expressed opinions upon this subject that the deposits are exudative fibrin. The illustrations which *Neumann* has presented in his work are in no manner confirmatory of his view, but enable us rather to affirm that *Neumann* had before him in his preparations exudative fibrin.

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See also §§ 89 and 92.

§ 92. When the inflammatory exudate is made up chiefly of leucocytes, there is produced within the tissue a **small-celled infiltration**

FIG. 205.—Purulent bronchitis, peribronchitis, and peribronchial bronchopneumonia in a child one year and three months old (Müller's fluid, hæmatoxylin, eosin). *a*, Purulent, *b*, mucoid bronchial contents; *c*, c_1, bronchial epithelium infiltrated with round cells and partly desquamated; *d*, infiltrated bronchial wall with greatly dilated blood-vessels; *e*, infiltrated peribronchial and periarterial connective tissue; *f*, alveolar septa, in part infiltrated with cells; *g*, fibrinous exudate in the alveoli; *h*, alveoli filled with exudate rich in cells; *i*, alveoli filled with exudate containing few cells; *k*, cross-section of a pulmonary artery; *l*, bronchial, peribronchial, and interacinous vessels showing marked congestion. × 43.

(Figs. 191, *b*; 205, *d*, *e*, *f*) which under certain conditions may be so marked that the structure of the tissue is more or less obscured. If *polynuclear leucocytes* or **pus-cells** are present in large numbers in the fluid

FIG. 206.—Section of a smallpox pustule (injected hæmatoxylin preparation). *a*, Horny layer; *b*, stratum mucosum of the epidermis; *d*, cutis; *e*, smallpox pustule; *f*, cavity of the pock, containing at f_1 pus-corpuscles; *g*, interpapillary remains of epithelium infiltrated with pus-corpuscles; *h*, papillary bodies infiltrated with cells; *i*, umbilication with thin pock cover; i_1, edge of the pock, the roof at this point consisting of the horny and transitional layers. × 25.

exudate on the surface of a mucous membrane or external wound that the exudate is white or yellowish-white in color and of a milky creamy consistence, it is called **pus**, and such an inflammation is de nated a **purulent catarrh** (Fig. 205, *a*). A persistent marked secre is termed a *blennorrhœa*. Collections of pus in the body-cavities— example, the pericardial, pleural, or joint cavities—give rise to *puru effusions* or **empyemata**. If within a blister arising through the lic faction of the epithelial layers beneath the horny layer of the epider there takes place a marked collection of leucocytes, the fluid beco more and more turbid, white, purulent, and the vesicle becomes chan into a **pustule** (Fig. 206, f_1).

When leucocytes collect in such large numbers within a tissue as

FIG. 207.—Embolic abscess of the intestinal wall with embolic purulent arteritis, and embolic arte in cross-section (alcohol, fuchsin). *a*, *b*, *c*, *d*, *e*, Layers of intestinal wall; *f*, remains of arterial wall, section; *g*, embolus, surrounded by pus-corpuscles lying within the dilated and partly suppurating ar *h*, parietal thrombus; *i*, periarterial purulent infiltration of the submucosa; *k*, vein showing marked gestion. × 28.

give it a white, gray-white, or yellowish-white color the process assu the character of a **purulent infiltration**. Should this be followed liquefaction and dissolution of the tissue the process results finally **tissue-suppuration** and **abscess-formation** (Fig. 207, *i*)—that is, in formation of a cavity filled with pus.

When purulent infiltration and tissue-suppuration occur on the s face of an organ—for example, on a mucous membrane (Fig. 208, *c g*)—the process leads to a superficial loss of substance—an **ul** The formation, through suppuration, of duct-like cavities gives rise to **tulous tracts.**

The liquefaction of the tissues, which is designated as suppurati

is possible only under the condition that they die. This tissue-necrosis is usually present before the occurrence of suppuration, and is caused by the specific action of the agent exciting the inflammation. The tissue may, however, die only during the course of inflammatory infiltration and then liquefy.

If an accumulation of pus-corpuscles is associated with an abundant collection of fluid, the **exudate** is spoken of as **seropurulent**; and such an exudate, when infiltrating the tissues, is often designated **purulent œdema.** The rapid spread of a purulent or seropurulent inflammation over wide areas—for example, through extensive areas of subcutaneous or submucosal tissues—is known as **phlegmon** (Fig. 209, *c*, *d*). This leads very often to the formation of extensive pus-cavities, in which there lie shreds of disintegrating tissue infiltrated with pus.

The association of serous exudation and fibrin precipitation with suppuration leads to the formation of **fibrinopurulent exudates** (Fig. 203, *d*, *e*); and effusions into the body-cavities, and meningeal exudates, as well as croupous exudates on mucous surfaces and in the lungs, and also phlegmons may bear this character. It is to be noted, however, that with the increase of suppuration the formation of fibrin becomes decreased, and the masses of coagula already present dissolve. The fibrin-masses infiltrated with pus are white and easily torn.

Suppurations and the associated formation of abscesses and ulcers are in the majority of cases caused by **bacteria,** most frequently by the *Staphylococcus pyogenes aureus*, *Streptococcus pyogenes*, and the *Gonococcus*;

FIG. 208.—Suppuration and necrosis of the mucosa of the large intestine in dysentery (Müller's fluid, hæmatoxylin, eosin). Section through the mucosa (*a*) and submucosa (*b*) of the large intestine; *c*, muscularis; *d*, interglandular, d_1, subglandular infiltration of the mucosa; *e*, focus of infiltration in the submucosa; *f*, infiltrated upper glandular layer undergoing desquamation; *g*, ulcer with infiltrated base. × 25.

but suppurations due to *Actinomyces*, *Bacillus typhi abdominalis*, *Diplococcus pneumoniæ*, or the *Bacterium coli commune*, are not rare. The staphylococci generally produce localized inflammations; streptococci, on the other hand, phlegmonous. The presence of certain bacteria (*Bacillus phlegmones emphysematosæ*, Fränkel; *Bacillus aërogenes capsulatus*, Welch) may cause the formation of **gas** (*gas-phlegmon*). Suppuration is sometimes ectogenous, sometimes lymphogenous or hæmatogenous; and in the last case often bears the character of a metastatic process (Fig. 207).

Of the **chemical substances** which, when introduced into the tis can produce suppuration may be mentioned mercury, oil of turpent petroleum, five- to ten-per-cent. solutions of silver nitrate, creolin, toxin, dilute croton-oil, and sterilized cultures of various bacteria, in which the bacterial proteins are the active agents. The suppurations produced by chemical substances differ from those produced by infection, in that they heal more easily, do not spread in the tissues, and do not give rise to metastases, and through the fact that their products when inoculated possess no virulence.

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FIG. 209.—Phlegmon of the subcutane sue with formation of a vesicle through (Müller's fluid, hæmatoxylin, eosin). a, C b, epidermis; c, infiltrated fat tissue; d of pus; e, cellular foci in corium; f, sub lial vesicle due to œdema. × 30.

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See also §§ 89–91.

§ 93. As was explained in § 92, suppurative inflammation always leads to tissue-necrosis; but this necrosis is immediately lost sight of in the presence of the liquefaction and dissolution of the tissues which form the characteristic feature of suppuration. In other forms of action upon the tissues, there may occur a more extensive tissue-necrosis, recogniz-

FIG. 210.—Necrosis of the epithelium of the epiglottis (Müller's fluid, hæmatoxylin). *a*, Living epithelium with well-stained nuclei; *b*, necrotic epithelium with nuclei not staining; *c*, leucocytes lying in the epithelium; *d*, hyperæmic, inflamed, and infiltrated connective tissue. × 300.

able even to the unaided eye, which is not followed by suppuration, but on the other hand is characterized by the fact that the necrotic portions of the tissue remain unchanged for a long time, and only relatively late are removed through sequestration and sloughing or through absorption. Since the tissue-necrosis in such a case forms the chief feature, the condition may be appropriately designated a **necrotic inflammation.**

The tissue-necrosis associated with inflammation may be caused by caustic **chemicals, high** or **low temperatures,** and **ischæmia,** as well as by **infection** (typhoid fever, diphtheria, dysentery, and tuberculosis).

The necrosis of the tissue may appear first of all as the immediate effect of the injurious action, the inflammatory exudation following later, and being confined to the region adjoining the necrosis; this is especially the case after the action of corrosive substances, and high temperature, and in ischæmia. In other cases, which belong chiefly to the infections, an inflammation is first established, the inflamed and infiltrated tissue later becoming necrosed. In tuberculous infections the necrosis occurs only after the tissue-proliferation has developed and has existed for some time.

Necrotic inflammations are most frequently seen on the mucous m branes, and are here usually called **diphtheritis**, particularly those w are caused by infection. The necrosis may at first affect the epitheli which in consequence loses its nuclei (Fig. 210, *b*) and later acquires a lumpy appearance. If there are formed white, opaque patches upon the mucous membrane, as in the pharynx in diphtheria, the condition may be spoken of as *epithelial* or *superficial diph theritis.* Usually, however, the designation *diphtheritis* is applied only to tissue necroses in which the *inflamed* and *infiltrated connective tissue undergoes necrosis* (Fig. 211, *a*), and becomes converted into a lumpy or granular mass without nuclei, or into a more homogeneous mass containing fibrin, in which the structure of the tissue can no longer be recognized.

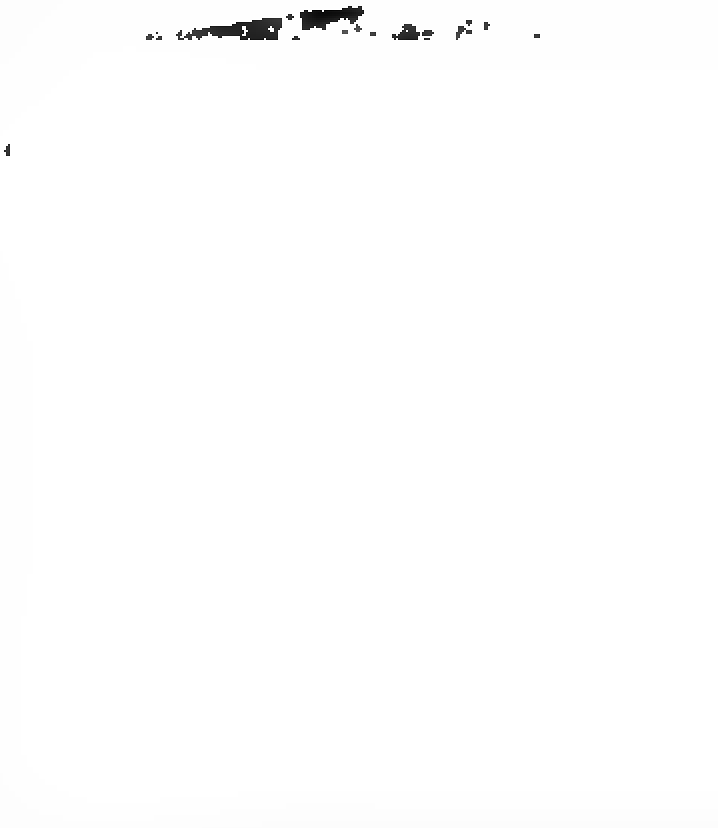

FIG. 211.—Bacillary diphtheritis of the large intest dysentery (alcohol, gentian violet). *a*, Necrotic port the glandular layer of the mucosa, infiltrated with bac intact inflamed mucosa; *c*, muscularis mucosæ; *d* mucosa; *e*, colonies of bacilli; *f*, glands with living e lium; *g*, glands with necrotic epithelium and bacilli; *h* nective tissue infiltrated with cells; *i*, blood-vessels. ×

Diphtheritic sloughing of the tissues of a mucous membrane is observed particularly often in the intestine (Fig. 211), but occurs also in o mucous membranes, as in those of the vagina, the descending uri passages, and the region of the throat, where the tonsils are especi frequently aff ed, etc. The erotic tissue fo white, or gray white, or, thro the admixture blood or bile other impurit dark green, yell brown, or oth wise colo sloughs, which surrounded by r dened and infla tissue. If so time has alre elapsed since formation, and liquefaction of tissue at the bou ary between t

FIG. 212.- Section of the uvula in pharyngeal diphtheria with croupous deposits (alcohol, aniline brown). *a*, Normal epithelium; *b*, connective tissue of the mucous membrane; *c*, reticulated fibrin; *d*, connective tissue of mucosa infiltrated with coagulated fibrin and round cells, and partly necrotic; *e*, blood-vessels; *f*, hæmorrhage; *g*, clumps of micrococci. × 75.

living and dead tissues has occurred, with a separation of the latter, the necrosed parts form loosely attached or wholly free deposits lying on the surface of the membrane, these consisting at times only of small flakes, at other times of larger sloughs.

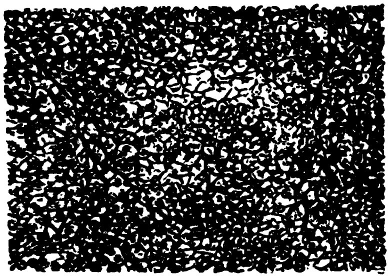

FIG. 213.—Diphtheritic necrosis within a swollen mesenteric lymph-gland, in typhoid fever (alcohol, fibrin-stain). Fibrin network between the necrotic cells. × 300.

Diphtheritis of mucous membranes may be associated with croupous deposits (Fig. 212, *c*, *d*), so that the tissue-necrosis (*d*) may be covered over with fibrin (*c*).

Wound-granulations may also necrose in the same way as do inflamed mucous membranes; such a condition may therefore be called ***wound-diphtheritis.***

Acute tissue-necroses caused by infection occur in the case of the internal organs, chiefly in the lymph-glands (Fig. 213), spleen and bone-marrow, and are characterized by the formation of opaque grayish-white, yellowish, or dirty-gray sloughs. Not infrequently fibrinous exudations are seen within the necrotic tissue (Figs. 212, *d*; 213).

In the necrosis caused by tuberculosis the destruction of the tissue occurs gradually, and bears the character of a **caseation.**

When an inflammatory focus contains bacteria which excite putrid decomposition of albuminoid bodies, the inflammation may take on the **character of a putrid gangrene;** and the tissue may disintegrate into a dirty gray or black, tinder-like mass which gradually dissolves and gives off an extremely disagreeable odor. Gas-bubbles are also sometimes developed in the focus. (See § 92.)

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See also §§ 89–92

II. The Termination of Acute Inflammation in Healing.

§ 94. Should there occur in any tissue whatsoever an acute inflammation, sooner or later there always arise processes which have in aim the

removal of the changes established and a restoration of the degene tissue, and which may therefore be regarded as **processes of repair** the cause which excited the inflammation is no longer present, processes consist essentially in the *cessation of the pathological exu* and its replacement *by the normal vascular secretion*, the *removal or al tion of the exudate present and of the necrotic tissue*, and the *restoration destroyed tissue*. If the *exciting cause of the inflammation* is still prese the tissue and active, it must be *removed or rendered inert*.

The **cessation of the alteration of the vessel-walls** is brought through the restoration of the normal blood-supply to the damaged b vessels, so that the nutrition of the vessels again becomes normal. alteration was slight, and if the exciting cause of the inflammation acted only for a short time—if it is the case, for example, only o brief action of a trauma, or high temperature, or chemical substance was quickly removed—the restoration of the vessels may take plac very short time, i.e., in a time that may be measured in minutes and h

When the exciting cause of the inflammation acts for some leng time—as, for example, in the case of bacteria which live and multip the tissues, or if changes are brought about through the inflamm itself, which act in such a manner as to alter the vessels—if ther been, for example, a tissue-necrosis—the vessels are subjected for time to a continued harmful action, which hinders the complete res tion of their functions.

FIG. 214.—Phagocytes from granulation tissue with included leucocytes and fragments of su limate, Biondi's stain). *a*, Round, *b*, spindle, fibroblast with leucocytes; *c*, *d*, *e*, fibroblasts contai mains of leucocytes. × 500.

The **absorption of the exudate** occurs in many cases easily quickly, in that it is taken up by the lymph-stream, eventually al the blood. This takes place most quickly in the case of serous exu yet in many places fibrinous exudates may also be quite rapidly rem but this occurs only when the coagula soon liquefy. For exampl coagulated exudate in the lung may be liquefied and made capa absorption through the action of a *proteolytic enzyme* (Müller) that most probably from the leucocytes. The absorption of exudates is often aided by **phagocytes**, that is, through the activity of amœboid present in the inflamed area, in taking up corpuscular substance destroying them. Thus, for example, large mononuclear cells (m phages) lying within the inflamed area may take up through boid movement polynuclear leucocytes (Fig. 214, *a*, *b*) and destro digest them (*c*, *d*, *e*). In the same manner red blood-cells and disintegration-products may be taken up (Fig. 115). Firmer fibr exudates such as are formed especially upon the serous membrane also large collections of pus, usually offer considerable resistance t sorption and are the cause of the prolonged course of the inflamm although the character of this may become changed from what it w

the beginning. In very many cases absorption is accomplished by the simultaneous substitution for the exudate of embryonic tissue which later becomes changed into connective tissue.

The **sequestration and absorption of necrosed tissue,** with the exception of the casting-off of dead epithelium, which may be very quickly accomplished, always require a certain length of time, which varies according to the nature, situation, and extent of the necrosed tissue. In general, the inflammation persists as long as necrotic tissue is still present. *Superficial necrosed tissues may be cast off after sequestration*—that is, after the separation of the dead from the living tissues. In the case of deep-seated tissue-necroses in which the tissue does not soon undergo total liquefaction, *absorption* is usually slow, and is brought about through a gradual substitution of living tissue for the dead. **Phagocytosis** often takes place also in the absorption of necrotic tissue. Fatty products of disintegration, which have a positive chemotactic action upon the amœboid cells, are taken up in large amounts, so that *fat-granule spherules* are formed (see Fig. 69).

The **regeneration of the degenerated tissue** is dependent, for its occurrence, partly upon the degree and extent of the degeneration, partly upon the nature of the tissue, and partly upon the mode of action of the agent exciting the inflammation.

If the tissue-cells of the inflamed area are but slightly degenerated, they are quickly restored when the nutrition becomes normal. If single cells are lost but the organization of the whole is not disturbed, there can take place in most tissues a rapid renewal of cells through a regenerative growth of the remaining cells. This is true particularly of the different forms of connective tissue, the surface epithelium, liver- and kidney-cells, while ganglion-cells, bone-cells, cartilage-cells, and heart-muscle cells possess but little or no power of regeneration (see Chapter VI.). Extensive destruction of tissue with solutions of continuity, wounds, fractures, suppurations, necrotic inflammations, etc., lead to tissue-proliferations, which are indeed sufficient to close the defect, but for the greater part do not lead to a restoration of the normal tissue, but to the formation of a tissue of a lower grade, which in its earliest stages is known as **granulation tissue,** in its mature form as **cicatricial tissue.**

With the entrance of regenerative proliferation and the formation of granulation tissue, there appears in the course of the inflammation a phenomenon which later gives to the inflammation an especial character, so that it may be designated a **proliferating inflammation.**

The **phenomena of proliferation** begin in inflamed tissues, at the earliest after eight hours, but are usually first clearly recognizable after from twenty-four to forty-eight hours.

In general, they appear the more rapidly the milder the inflammation and the more quickly the pathological exudation is overcome or diminished. Suppuration, necrosis, and gangrene of the tissues hinder proliferation and retard the beginning of repair, or at least confine the reparative processes to the neighboring tissues.

Every tissue capable of proliferation furnishes formative cells for tissue of its own kind or for one closely related to it. Pus-corpuscles are not formed by the tissue-cells; on the other hand, *cells newly developed from the tissue-cells by proliferation may become mixed with the exudate, degenerate in the same, and die.* Thus not all the cells newly developed through proliferation fulfil their function of producing new tissue.

The **removal of the exciting cause of inflammation** takes place very

differently in different cases, and depends in the first place upon the nature of the cause. Many traumatisms and thermal influences act but for a short time, and have no further influence upon the course of the inflammation. Many substances acting chemically may be quickly taken up by the tissue-juices and made inert, or excreted, while others remain locally active for a longer time. *Insoluble foreign bodies in the form of dust* which have penetrated into the tissue, as, for example, into the lungs, are for the greater part taken up by *phagocytes* and carried away (see § 21) and either deposited here or there, or are removed from the body. Of the bacteria exciting inflammation, many soon die as the result of *bactericidal substances* formed in the diseased area (see § 31). *The destruction of the bacteria takes place partly in the tissue-fluids* and partly by *phagocytosis*, the bacteria being taken up by the cells either alive or having first been killed are then digested. Of the bacteria producing inflammation, many soon die, while others live and constantly produce new generations which in turn cause new inflammation, often in such a way that in the first diseased focus the inflammation may subside and healing take place, while in the neighborhood, or even in more distant regions, *metastatic inflammations* develop.

On account of the great differences which exist both in the nature and the behavior of the exciting cause of the inflammation, as well as in the course of the inflammatory tissue-degeneration and the exudation, and in the course of the healing processes, it is easy to understand that the whole course of an inflammation, even to its termination in healing, may vary greatly in different cases, so that all the possibilities of its course can hardly be reviewed. At the same time it is not difficult to comprehend the decline of the different forms of inflammation, since ultimately the whole process is always made up of the same factors—that is, of tissue-degeneration, pathological exudation, and of proliferative processes, the last of which are calculated to remove the disturbances caused by the first two factors.

Neumann groups under the term inflammation all those phenomena which develop locally after a primary tissue-lesion, and are directed toward the healing of this lesion. According to this view, regeneration is, therefore, the most important part of the inflammatory process, in that it is especially adapted to restore the defect of tissue caused by the primary tissue-lesion, or, as *Neumann* puts it, to restore the uninterrupted continuity of the tissue. Such an identification of inflammation with regeneration I hold as inadmissible, in the first place because tissue-regenerations occur which clinically and anatomically in no way bear the character of an inflammatory process. Then also the inflammatory pathological exudations cannot be regarded as phenomena that can be compared with regeneration, and that, like it, have for an end the healing of the primary tissue-lesion. Even if they act favorably in individual cases (the production of bactericidal antibodies, formation of complement by leucocytes), this is not always true. Much more often do they cause serious damage which increases that established by the primary tissue-lesion, and often enough form a hindrance to the rapid establishment of the healing process.

The phenomena of **chemotropismus** or **chemotaxis,** that is, the attraction or repulsion of motile cells by chemical substances soluble in water, were first observed by *Strahl* and *Pfeffer*, who carried out observations on the myxomycetes, infusoria, bacteria, spermatozoa, and zoospores. Investigations by *Leber*, *Massart*, *Bordet*, *Borissow*, *Gabritschewsky*, and others have shown that the leucocytes likewise are attracted by chemical substances (*positive chemotropismus* or *chemotaxis*) or are repelled by them (*negative chemotropismus*). In particular do products of the vital activities of the fission-fungi (*Leber*, *Massart*, *Bordet*, *Gabritschewsky*), or the bacterial proteins, that is, albuminous bodies of the dead bacterial cells (*Buchner*), even in a great dilution (according to *Buchner*, pyocyaneus protein acts even in a three-hundred-fold dilution), possess a positive chemotactic action. According to *Buchner*, this property is shown also by gluten-casein from wheat-gluten and legumin, aleuronate, glue from bones, and alkali

albuminates from peas, while ammonium butyrate, trimethylamin, ammonia, leucin, tyrosin, urea, and skatol show negative chemotaxis.

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See also §§ 95 and 97.

III. Inflammatory New-formation of Tissue; Healing of Wound Substitution of Exudates and Tissue-necroses by Conne Tissue.

§ 95. The **inflammatory proliferation of tissue** is essentially a r erative process which aims to compensate for the tissue-lesion proc by any cause of inflammation. Especial conditions may so infl the process that they not rarely lead to hyperplastic proliferations c connective tissue which fail to accomplish this purpose and cause injury, and this is especially the case when the cause of inflamm (chronic infection) or the persistence of the residues of acute infla tion (exudates, abscesses, tissue necroses) keep up a chronic cond of inflammation.

The inflammatory new-formation of tissue is brought about essen in the manner described earlier (§§ 81–86) of the regenerative hyperplastic proliferation of tissue. They may be distinguished simple regenerations by the fact that they, at least in a part of course, are accompanied by *circulatory disturbances* and *pathol exudations*, especially by an *immigration of lymphocytes and leucocytes* that these have a modifying action upon the course of the process.

The granulation tissue which is formed during the course of an in mation is nothing more than an **embryonic tissue arising through proliferation and infiltrated with leucocytes and lymphocytes**

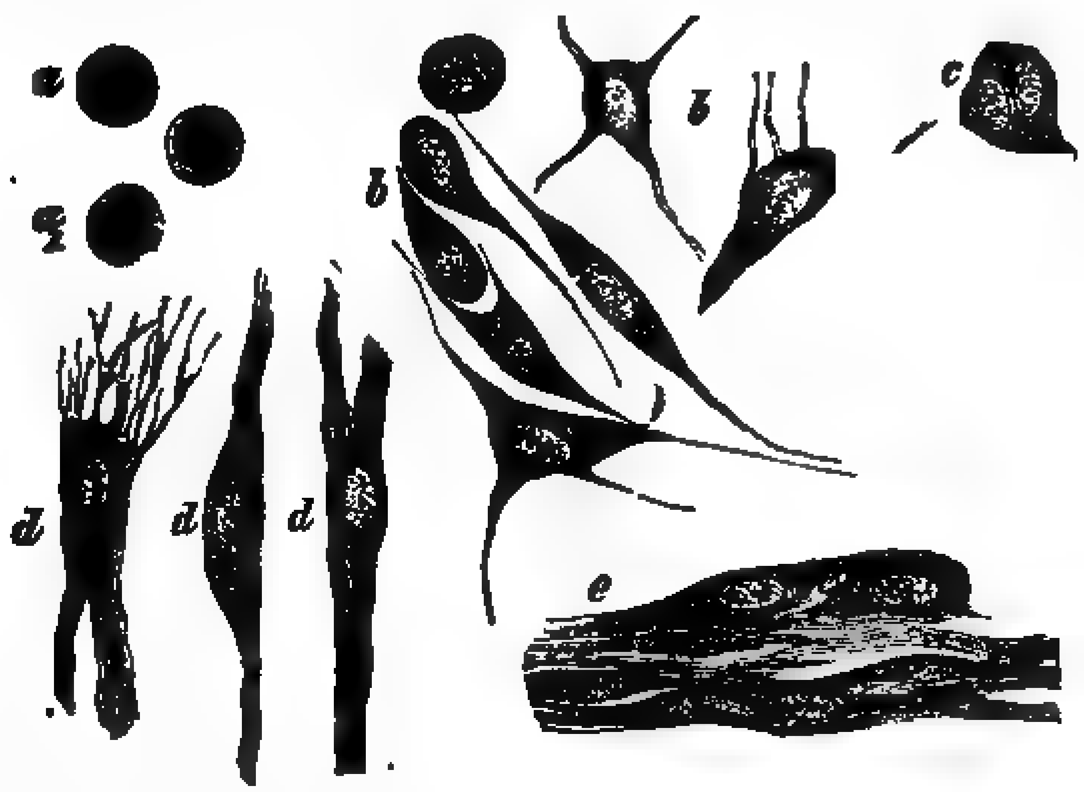

FIG. 215.—Isolated cells from a wound-granulation (Müller's fluid, picrocarmine). a, Monon a_1, polynuclear leucocytes; b, different forms of mononuclear fibroblasts; c, fibroblast with two c_1, multinuclear fibroblast; d, fibroblasts in the stage of connective-tissue formation; e, fully dev connective tissue. × 500.

the beginning it consists essentially of *cells and new-formed blood-v* which at first find their support in the ground-substance of the tissue which they pass out, but soon form for themseles a *new ground-subst*

The cells of the granulation tissue are in part **proliferated tis cells** (Fig. 215, b, c, d), in part **polynuclear leucocytes** (a_1) and **mon clear lymphocytes** (a). In most cases the proliferated cells are co

tive-tissue cells which later produce connective tissue (*d*, *e*) and are therefore known as **fibroblasts.** The granulation tissue, however, may also contain the derivatives of other tissues, for example, of the periosteum, marrow-tissue, and muscle-tissue, in the form of *osteoblasts*, *chondroblasts*, and *sarcoblasts*, which are able to form bone, cartilage, and muscle. Further, newly formed *glandular epithelium* may occur within glands, while in mucous membranes and in the outer skin new-formed *surface epithelium* may be found in or upon the granulation-tissue, these ~~being~~ able to produce *epithelial-tissue formations.* The **fibroblasts of the granulation-tissue** are large polymorphous cells, with clear nuclei (Fig. 215, *b*), and in part possess long processes. Young forms without processes may resemble epithelial cells and are therefore classed with the so-called epithelioid cells. With the help of their processes they can push into the tissue spaces, but usually show no lively amœboid movements.

In the further development of the granulation tissue the **fibroblasts form connective-tissue fibrillæ,** a portion of the protoplasm taking on

Fig. 216.—Scar fifteen days old (Maximow, l. c.). *a*, Fibroblasts; *b*, polymorphous lymphocytes (polyblasts); *c*, unchanged lymphocyte (polyblast). × 500.

a fibrillar appearance, or first becoming more homogeneous and then producing fibrillæ (Figs. 215, *d*, *e*; 216, *a*; 217, *a*).

The **polynuclear leucocytes** of the granulation tissue (Fig. 215, *a*) arising from the blood are not capable of further development and either wander farther or finally die, particularly those which as *pus-corpuscles* collect on the surface of the tissue or in abscesses. If bacteria are present in the tissue (streptococci, staphylococci, gonococci, anthrax-bacilli, etc.) the leucocytes may act as *phagocytes* (*microphages*) and aid in the destruction of the bacteria.

The **lymphocytes** and **mononuclear leucocytes** of the granulation-tissue are cells which for the chief part arise from the blood, although such cells may later be present in the tissue, and, increasing by division,

may be mingled with the cells of the exudate. Many of them d
the granulation tissue, as do the polynuclear leucocytes; or, on the
hand, they may change into various cell-forms, and from this poi
view they may be designated **polyblasts.**

Enlargement of the cell-protoplasm and a certain enlargement
clearing of the nucleus give them the character of *epithelioid cells*
usually they are of smaller size than fibroblasts and their nuclei

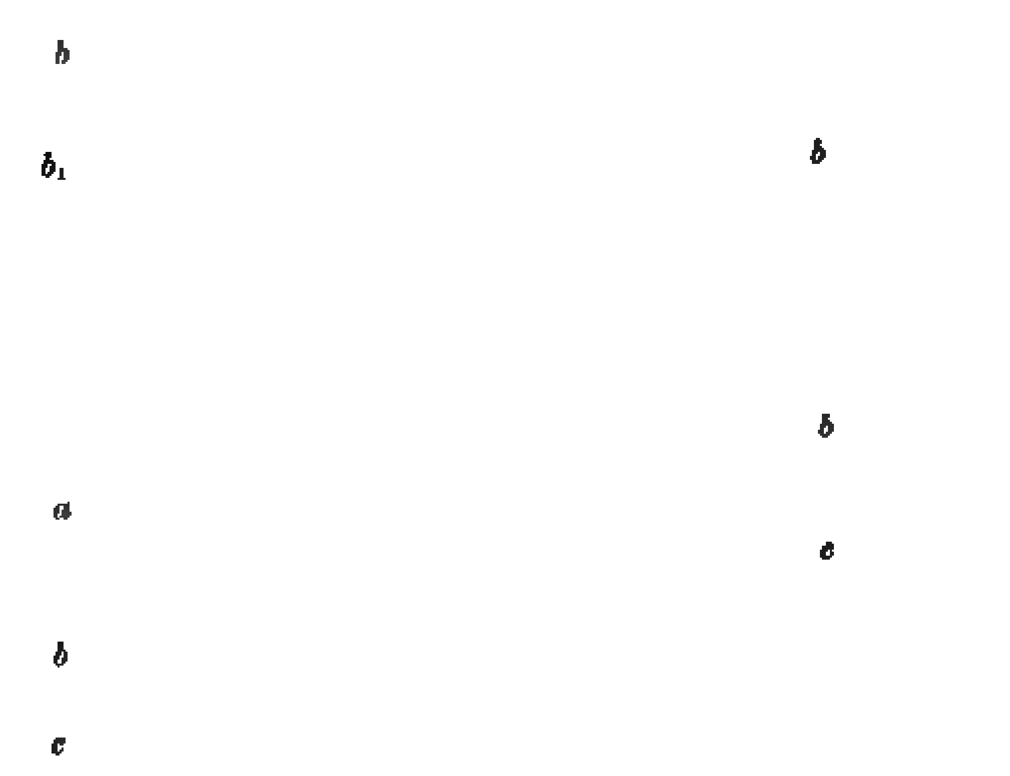

FIG. 217.—Tissue from a scar sixty-five days old (Maximow, l. c.). *a*, Fibroblasts; *b*, b_1, s
formed lymphocytes (polyblasts), with elongated nuclei embedded in the tissue; *c*, plasm
× 500.

darker (iron-hæmatoxylin or methylene blue) than those of the f
blasts.

By sending out plump pseudopodia they may take on the *most varied f*
(Fig. 216, *b*). On the surface of smooth foreign bodies they may
form an epithelial-like deposit or covering.

In the development of fibrous cicatricial tissue they may be embe
as *permanent elements* of the same in the form of *spindle cells* which fi
can be distinguished only with difficulty or not at all from the ordi
connective-tissue cells (Fig. 217, *b*, b_1). Occasionally they assume
a character corresponding to that of the so-called *klasmatocytes* of Ra
(Fig. 218, *b*), that is, they form spindle or branched cells, coa
granular, showing many vacuoles and often containing granules stai
metachromatically (polychrome methylene blue). Further, they
assume the appearance of *plasma-cells* (Figs. 217, *c*, 218, *c*), that is, r
or irregularly formed cells having an eccentric nucleus and a bright
tral and a dark granular peripheral plasma. These plasma-cells
die or take on the appearance of the first-named forms.

The **derivatives of the lymphocytes**, *polyblasts*, are those cells w
show the greatest activity in the granulation tissue as **phagocytes**,

not only take up bacteria but also cells, red blood-cells and leucocytes (Fig. 214), and destroy them or carry them away.

They have also an especial inclination to form **multinucleated giant-**

d

FIG. 218.—Plasma cells and klasmatocytes within scar tissue, forty days old (Maximow, l. c.). *a*, Fibroblasts; *b*, klasmatocytes; *c*, plasma cells, *d*, blood-vessel. × 500.

cells, and, indeed, *syncytial forms*, that is, through the *confluence of cells lying in close contact.* This is most frequently observed when larger or smaller foreign bodies or necrotic portions of the tissue lie within the granulation tissue (Fig. 219, *d*), and they are therefore designated as **foreign-body giant-cells.** Soluble substances, for example, catgut sutures or necrotic muscle-substance, can be gradually dissolved by them.

The presence of certain forms of bacteria (tubercle-bacilli and lepra-bacilli) can also lead to their formation.

The **blood-vessels of the granulation tissue** arise through offshoots from the old vessels (see Fig. 166), which very early, even at that time in which the immigration of leucocytes takes place (Fig. 220, *b*, b_1), show

FIG. 219.—Dog's hair encapsulated in the subcutaneous tissue (alcohol, Bismarck brown). *a*, Hair; *b*, fibrous tissue; *c*, proliferating granulation tissue; *d*, giant-cells. × 66.

proliferative processes (*a*), and in the formation of granulation tissue take on a very lively proliferation. The young granulation tissue, as a result, becomes permeated by a great number of blood-vessels, so that it acquires a red appearance. During the transformation of the granulation

tissue into connective tissue or **scar-tissue** there occurs an **obliter** *of the vessels* and the scar becomes pale.

The structure of the granulation tissue, the origin and the fate o cells contained in it, have been for decades the object of investigation and discu and even to-day not all of the questions can be regarded as solved. It has been de strated beyond doubt, however, that *the builders of cicatricial tissue*, the *fibroblast* *derivatives of the fixed connective-tissue* further, it is certain that the *polynuclear cytes* arise from the blood and undergo n ther development. The origin of the *mononuclear cells* which resemble the ly cytes and the mononuclear leucocytes o blood is still a matter of dispute, as is al rôle which they play within the granul tissue. Even in the year 1876, on the g of experimental investigations, I expresse opinion that they were *capable of a f development into epithelioid cells* and th the time of their formation and transform they exert *phagocytosis* and take up other and digest them and that they can b changed into *permanent elements* of cica tissue. I have further demonstrated that especial conditions they form *syncytial cells*.

FIG. 220.—Cross-section of blood-vessel from the deep layers of the skin, forty hours after painting the skin of a rabbit with tincture of iodine (Flemming's solution, safranin). *a*, Endothelial cells with mitoses; *b*, b_1, leucocytes. × 350.

Maximow, through investigations carried on in my laboratory in the years 1902, has confirmed the view that the mononuclear leucocytes and lymphocytes, passing out from the blood-vessels, may undergo further development, and has de strated that within the cicatricial tissue they take on in part the appearance of *matocytes, plasma-cells*, and *mast-cells*, also in part appearances similar to those *ordinary fixed connective-tissue cells*, so that finally differentiation of the two cell- is no longer possible. They also change in part to fixed connective-tissue cells, b not produce, as I formerly assumed, the fibrillary ground-substance.

With reference to the varied forms which these cells show, *Maximow* has desig them *polyblasts*. Much more appropriate would be the term *polymorphocyt poikilocytes*, although the latter term is in common use for various forms of degene red blood-cells.

The differentiation of the different cell-forms as given above, rests essentially differences in the structure of the protoplasm. **Plasma cells** (*Unna*) or the "kr zellen" (*von Marschalko*) are mononuclear, round or oval, at times elongated cell stain intensely with methylene blue and possess an eccentrically placed nucleus sh a chromatin network and five to eight chromatin granules. At the periphery o cell the protoplasm is more densely clumped, so that there is formed a lighter surrounding the nucleus. The *klasmatocytes* (*Ranvier*) are spindle-shaped, branc stellate cells with blunt or swollen ends and a granular protoplasm that often co little vacuoles. The *mast-cells* (*Ehrlich*) are round or flat or spindle-shaped cells, numerous distinct coarse granules that, with the basic aniline stains, show an in metachromatic reaction.

Cells of the character of lymphocytes, leucocytes, plasma-cells, klasmatocyte mast-cells occur even in normal tissue and are regarded by some authors as es forms of tissue cells and by others as cells arising from the blood. According to we know of their occurrence the most correct view is probably that which regards as different stages of development of a mesenchymal group of cells of an especia that are to be separated from the tissue-building fixed cells, and to this group should be added also the polynuclear leucocytes and the eosinophile cells. C stages of development are present in the blood, others are found in the tissue and, in partly in especial tissue-formations (lymphadenoid tissue, bone-marrow), and par ordinary connective tissue. Under certain conditions the individual forms may into one another, as, for example, lymphocytes may become transformed into p cells and klasmatocytes into mast cells.

The mononuclear cells that collect so quickly in an *inflammatory area* arise, f chief part, from the blood-vessels. When the given cell-group occurs at the pl inflammation (as, for example, perivascularly situated klasmatocytes or lymphoc they may increase by division and take part in the formation of the cellular collec In scar tissue, for example, polyblasts of the appearance of klasmatocytes may c again into cells corresponding to amœboid lymphocytes.

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See also § 94 and § 97.

§ 96. If upon any part of the body-surface there occurs an **open wound**, which does not become infected with bacteria or seriously injured in any way, the edges and base of the wound after twenty-four hours become deep-red and somewhat swollen. The individual constituents of the tissue can still be clearly recognized, only the tissue appears somewhat swollen, and here and there small shreds of necrotic tissue may be seen. On the second day the gelatinous condition of the tissues is more apparent, the outlines of the individual tissue-elements are effaced, and the color becomes grayish-red. On the wound there lies a reddish-yellow fluid. From the second day on there appear over the whole wound small red papules, which rapidly increase in number and size, become confluent, and after two to three days form a granular red surface—a **granulation surface.** This is covered with a more or less abundant wound-secretion, which forms a gray, gelatinous layer, later becoming more yellow and creamy. This layer consists of a *coagulable exudate* and numerous polynuclear leucocytes.

FIG. 221.—Wound-granulations from an open wound with fibrinopurulent covering (Müller's fluid, hæmatoxylin). *a*, Granulation tissue; *b*, fibrinopurulent layer; *c*, blood-vessels. × 135.

The changes which the surface of the wound shows are in the first two days dependent upon the local hyperæmia, and the infiltration of the tissue with cel-

lular and fluid exudate, and upon the swelling and liquefaction of the tissue; as early as the second day there is added thereto a tissue-proliferation with new-formation of vessels, leading to the development of **wound-granulations.** After a few days there will have developed in the wound a *granulation tissue* (Fig. 221, *a*) *consisting of fibroblasts and leucocytes, and rich in wide vessels* (*c*), and in which there very soon appears a *fibrillar ground-substance.* The leucocytes, which belong chiefly to the polynuclear form, are found in all the layers of the skin in fresh granulations, but heap themselves particularly in the superficial strata, and, *embedded in fibrin,* cover over the surface of the granulation tissue (*b*). The fibroblasts are found most abundantly in the deeper layers (Fig. 221, *a*), and here the new-formation of connective tissue proceeds most actively.

When a certain degree of fibrillæ-formation has been reached, the process comes to a standstill, the remains of the fibroblasts with their nuclei remain as fixed connective-tissue cells (Fig. 215, *e*), continue to live, and attach themselves to the surface of the bundles of fibrillæ. The process has then reached its termination—the *granulation tissue has become* **scar-tissue.**

In **open wounds of the skin,** when infection does not disturb the course of healing, the formation of granulation tissue lasts until the wound is again covered with epithelium. The regeneration of the latter proceeds from the edges, the epithelium gradually pushing itself over the granulations. With the formation of connective tissue the reproductive processes essentially terminate, but transformation processes continue in the cicatricial tissue for some length of time. Shortly after its formation the cicatrix is rich in blood and appears red; later it loses a portion of its vessels through their obliteration, becomes pale, and contracts to a volume much less than the original. Large scars of the skin show permanently a smooth surface, since the papillary bodies are not again formed or only imperfectly (Fig. 223, *e*). The tissue of the scar remains for several months abnormally rich in cells, but in the course of time becomes poorer in cells and harder, and comes to contain elastic fibres.

When the healing of a wound occurs in such a manner that the tissue-defect is closed by the formation of a granulation tissue visible to the naked eye, the process is designated *repair by second intention* (*per secundam intentionem*).

The **healing of incised wounds of the skin,** *whose edges, united by sutures, grow together by first intention,* takes place in essentially the same manner as the healing of an open wound by second intention; but the processes of inflammation, proliferation, and new-formation of tissue are less prominent, partly because they take place below the skin, and partly because they are of much less extent and intensity.

The result of such a cut is always a more or less abundant exudation on the edges of the wound, forming a coagulated mass often containing blood (Fig. 222, *c*), which glues together the opposing wound-surfaces. Very soon there arises an inflammatory infiltration of the edges of the wound, which varies greatly in different cases, and when the course of repair is aseptic never reaches any significant degree (*g*, *h*), attaining its maximum in from two to four days, diminishing from the fifth to the seventh day, and completely disappearing at or soon after the end of the second week. The inflammatory infiltration is usually greater in the neighborhood of the wound-sutures than at the edges of the wound.

As early as the second day regenerative processes of proliferation begin in the connective tissue and in the vessels, and lead, in the course of several days, to the formation of an embryonic tissue, which lies partly

in the spaces of the connective tissue at the edges of the wound (
222, *f*), and partly extending into the open space of the wound itsel
and here gradually grows into the coagulum which is present and rep
it. This tissue is usually present in varying quantity in different p
of the wound (Fig. 222), and may be entirely absent in places. Af
certain number of days, the time varying according to the size of

FIG. 222.—Healing of incised wound of skin united by suture (Flemming's solution, safranin). I
ation made on the sixth day. *a*, Epidermis; *b*, corium; *c*, fibrinous exudate, in part hæmorrhag
newly formed epidermis, containing numerous division-figures, and with plugs of epithelium ext
into the underlying exudate; *e*, division-figures in epithelium at a distance from the cut; *f*, prolif
embryonic tissue, developing from the connective-tissue spaces, and containing cells with nuclear di
figures, and in part also vessels with proliferating walls; *g*, proliferating embryonic tissue with leuc
h, focus of leucocytes in deepest angle of wound; *i*, fibroblasts lying within the exudate, one sho
nuclear division-figure; *k*, sebaceous-gland; *l*, sweat-gland. × 70.

wound, the thickness of the exudate between the edges of the wound
the intensity of the proliferation, the masses of embryonic tissue gro
from the edges of the wound blend together, and there follows the fo
tion of young connective tissue, which joins the edges of the woun
gether, and at the same time extends also into the old tissue, so tha
boundary between the old and the new tissue becomes indistinct.

While connective tissue is being formed in the deeper parts of
wound, the epithelial covering on the surface is also being regene
(Fig. 222), and indeed in this manner, that the epithelium pushes
the wound-surface, and through a continuous cell-division (*d*, *e*) f
an epithelial covering consisting of many layers. The epithelium

push across the wound-surface even before a new-formation of cells has taken place.

The young connective tissue of the scar uniting the edges of the wound is distinguishable for a long time from the neighboring older tissue through its richness in cells (Fig. 223, *d*, *f*), as well as through the finer fibrillation of its ground-substance; and in large incised wounds of the skin there may be found in it, here and there, after the lapse of

FIG. 223.—Cutaneous portion of a laparotomy cicatrix, sixteen days after the operation (Müller's fluid, hæmatoxylin, Van Gieson's). *a*, Epithelium; *b*, corium; *c*, subcutaneous fat tissue; *d*, scar in corium; *e*, new epithelial covering; *f*, scar in fat tissue. × 35.

weeks or even months, slight evidence of proliferation and inflammations. In general, however, transformation processes gradually occur in the blanching scar, so that its tissues come to approach more closely to the normal, and finally the place of the incision can no longer be easily recognized. If the wound heals by the interposition of abundant embryonic tissue, there may occur a defect of the papillary bodies (Fig. 223, *e*), so that the scar remains smooth.

§ 97. When there is found upon the surface of an **inflamed serous membrane** (Fig. 224, *a*) an **adherent layer of fibrin** (*b*), there usually develop quickly beneath it **granulation-formations.** The earliest beginnings of these can be seen as soon as the fourth day after the formation of the fibrinous deposit, and they consist at first of the appearance of *fibroblasts* (*f*) and polyblasts in the deepest layers of the fibrinous membrane. These arise through the proliferation of the connective-tissue cells of the affected serous membrane, and wander to the surface, and into the fibrin. In association with this phenomenon there follows very

soon a new-formation of blood-vessels, and in the course of days or weeks there is developed upon the surface a vascular embryonic tissu granulation tissue, which, when the overlying fibrin layer is very co pact, lifts this up *in toto* (Fig. 225, *b*, *c*); or penetrates into the interstices of the fibrin-membrane (Figs. 224, *f*; 226, *b*, *d*), and in the course of time replaces the fibrin. Remains of the fibrin (Fig. 226, *c*) may, however, often persist for a long time, weeks or months, within the granulation tissue.

FIG. 224.—Fibrin deposit and beginning formation of granul tissue in a fibrinous pericarditis five days old (Müller's fluid, h toxylin). *a*, Epicardium; *b*, fibrin-membrane; *c*, dilated, con vessels; *d*, round cells infiltrating the tissue; *e*, lymph-vessel filled cells and clots; *f*, fibroblasts within the deposit. × 150.

In the formation of the granulation tissue and the development of scar-tissue the epithelium (endothelium) of the serous membranes takes no part, since it produces no fib blasts. On the other hand, the products of the inflammatory prolife tion become covered later with epithelium.

The final result of the process is the formation of **connective tiss** which leads either to a *thickening* of the serosa which had been cove with fibrin, or to an *a sion of the opposing surf of the serous membrane* that the inflammation m be designated as *adhes* The result in individ cases depends partly u the amount of the fib deposit and partly u the situation of the aff ed organ, and its condi during the process of h ing.

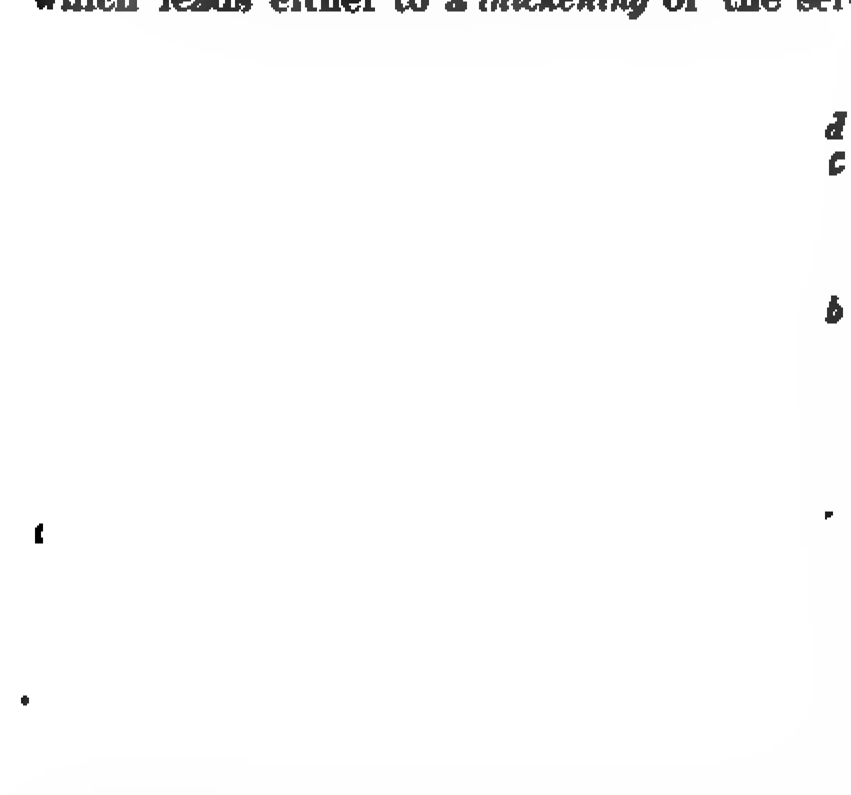

FIG. 225.—Development of granulation tissue in the pleura, in bronchopneumonia and pleuritis of fourteen days' duration (alcohol, Van Gieson). *a*, Hyperæmic, infiltrated pleura; *b*, very vascular granulation tissue; *c*, fibrin; *d*, pus-corpuscles, and granules of precipitated albumin. × 100.

Small deposits fibrin, limited to one face of the serous m brane, lead only to th enings of the sero which, becoming pale the obliteration of the sels, are represented fi ly by white thicken frequently designate **tendinous spots.** firm glueing together of two serous layers by an abundant deposit of fi leads also to a firm **adhesion** of the same through the abundant for

tion of connective tissue. In the case of a smaller amount of fibrin, and repeated rubbing of the membranes upon each other, there develop only loose *membranous* or *stringy adhesions*, which still permit the serous surfaces to move upon one another. Very large amounts of *fibrin* may also, under certain conditions, in part permanently resist absorption, so that they remain lying within the newly formed connective tissue, and then usually become *calcified*.

FIG. 226.—Formation of granulation tissue in the fibrinous deposits of a pericarditis several weeks old (Müller's fluid, hæmatoxylin, eosin). *a*, Epicardium; *b*, deposit on the epicardium, consisting of granulation tissue (*d*), and fibrin (*c*). × 40.

Coagulated exudates in the lungs may quickly become liquefied and *absorbed*, but it also happens that their removal may be associated with a connective-tissue proliferation, which leads to an *induration of the lung*. The proliferation proceeding from the lung tissue leads either to a thickening of the septa (Fig. 227, *a*, *b*) or extends into the exudate lying in the alveoli, in the form of an embryonic tissue (*d*, *e*), which later comes to contain newly formed blood-vessels (*g*).

Masses of coagula within blood-vessels, which are called thrombi, give rise, in case no infection occurs, to an inflammatory—that is, associated with cell-emigration—proliferation of the vessel-wall, a *proliferating vasculitis*. This process corresponds exactly to the inflammatory proliferation of the serous membranes. It is entirely immaterial whether the thrombosis has been caused by a preceding inflammatory process or by any other conditions, inasmuch as the presence of the mass of coagulum is sufficient to cause inflammation and tissue-proliferation.

FIG. 227.—Intraseptal and intra-alveolar formation of connective tissue in the lung (alcohol, hæmatoxylin). *a*, Thickened fibrocellular alveolar septum, in part infiltrated with round cells (*b*); *c*, fibrinocellular exudate in the alveoli; *d*, intra-alveolar formative cells; *e*, strand of spindle-cell fibroblasts; *g*, intra-alveolar newly formed blood-vessel. × 200.

The first change intro-

duced in the **substitution of the thrombus by connective tissue** is here also the appearance of *fibroblasts* (Fig. 228, *h*), which arise from the vessel-wall, and later, with the aid of vessels growing in from the vessel-wall and its neighborhood, form an embryonic tissue, which ultimately changes into connective tissue. The complete substitution of an obturating thrombus or embolus leads to the obliteration of the vessel-lumen by vascularized connective tissue (Fig. 229, *g*); the substitution of a parietal thrombus, on the other hand, results in formation of fibrous thickenings of the vessel-wall. As the result of

FIG. 228.—Development of embryonic tissue in a thrombosed fe[illegible] artery of an old man, three weeks after ligation (alcohol, hæmatox[illegible] *a*, Media; *b*, elastic limiting membrane; *c*, intima, thickened th[illegible] older inflammatory processes; *d*, coagulated blood; *e*, cellular infilt[illegible] of the media, *f*, of the intima; *g*, round cells, partly in the thro[illegible] partly between it and the intima; *h*, different forms of fibro[illegible] × 300.

FIG. 229.—Periphery of a healing pulmonary infarct (Müller's fluid, hæmatoxylin, eosin). *a*, [illegible] extravasate changed into a yellowish granular mass; *b*, necrotic alveolar septa without nuclei; *c*, [illegible] formed connective tissue; *d*, vascular granulation tissue within the alveoli; *e*, fibroblasts within [illegible] containing the residue of the hæmorrhage; *f*, artery; *g*, vascular connective tissue formed withi[illegible] artery at the place of the embolus. × 40.

imperfect substitution and liquefaction of the part not substituted, there arise strands and threads of connective tissue, which cross the lumen of the vessel. The calcification of portions of thrombi not replaced by connective tissue leads to the formation of vessel-stones (arterio- or phleboliths).

Necrotic tissue, which cannot be sequestrated and discharged externally, is also **replaced by a vascular connective tissue,** which becomes converted into **scar-tissue;** and this substitution takes place in the same manner as in the case of fibrinous exudates and thrombi. The requisite condition for this substitution is that the necrotic tissue shall contain no substances (bacteria) which hinder tissue-proliferation or excite severe inflammation. In general it is immaterial how the necrosis has occurred, and whether the necrotic tissue is free from exudate or is infiltrated with exudate or blood. The first phenomenon leading to healing is the association with the inflammatory exudate, in the neighborhood of the necrosis, of a tissue-proliferation, which produces **granulation tissue,** which grows toward the necrotic tissue (Fig. 229, *d*, *e*), dissolves it, and finally replaces it. If this process is not disturbed by any influence whatever, even very large tissue-necroses (for example, a hæmorrhagic infarct of the lungs) may in the course of weeks and months be made to disappear and may be replaced by connective tissue. It may also happen, however, that certain tissues resist absorption, or that the development of granulation tissue stops so early that remains of *the necrosed tissues persist and later become calcified.*

FIG. 230.—Fibroid area in heart-muscle. Section through a muscle-trabecula which has undergone fibroid change (Müller's fluid, hæmatoxylin). *a*, Endocardium; *b*, cross-section of normal muscle-cells; *c*, hyperplastic connective tissue rich in cells; *d*, atrophic muscle-cells in hyperplastic connective tissue; *e*, dense connective tissue, poor in nuclei and containing no muscle-cells; *f*, vein, in whose neighborhood muscle-cells are still preserved; *g*, small blood-vessels; *h*, small-celled infiltration. × 40.

When, as the result of an inflammation or ischæmia within an organ, only the more sensitive elements die—for example, epithelial or muscle cells—while the connective tissue remains intact, the absorption of the necrotic portions takes place very quickly, and there is formed within a short time a *scar* or *callus of connective tissue* (Fig. 230, *e*), in which the specific tissue-elements are lacking.

Pus is quickly *absorbed* from small abscesses, and the *defect closed by granulation and scar tissue.* Large amounts of pus may be absorbed from the body-cavities and from the lungs.

Abscesses cause in their neighborhood a **proliferation** of **granulation tissue** which leads to the formation of an **abscess-membrane.** The abscess-cavity may become obliterated through the absorption of the pus and the growing together of the granulation-membrane covering the walls of the cavity; the abscess finally heals and leaves a **scar.** Incomplete absorption may lead to thickening of the pus and later a *calcification* of the *residue.* If the pus does not become inspissated, the **abscess may persist** and in the course of time may be increased in size by secretion from its walls.

Empyemata may heal in a similar manner to abscesses through the absorption of pus. At the time of absorption the tissues enclosing the pus produce **granulation-** and **scar-tissue,** which may reach a considerable size when the process of absorption takes a long time (Fig. 232). When incompletely absorbed, *calcification of the thickened pus may occur.*

Foreign bodies, so far as they are absorbable and exert no specific influence upon their surroundings, are likewise dissolved, and replaced by connective tissue in the same way as are tissue-necroses or fibrin masses. If they possess accessible interstices, these may be penetrated by granulation tissue. If their mass cannot be absorbed, they become encapsulated.

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See also §§ 94 and 95.

IV. Chronic Inflammations.

§ 98. **Inflammation** is, according to its nature, an acute process, but various conditions may cause the phenomena of tissue-degeneration and exudation to persist for a longer time, and the inflammation becomes chronic.

The **causes of chronic inflammations** may be found, in the first place, in the fact that *in the course of an acute inflammation there occur changes which prevent a rapid healing.* In this sense, as may be deduced from the foregoing, act all large tissue defects and tissue necroses, as well as large masses of exudate which are with difficulty absorbable. When n e c r o t i c masses of tissue are not completely absorbable, as in the case of large pieces of bone, they may indeed become sequestrated, but persist as sequestra for years (Fig. 231, *a*), and keep up a constant inflammation. Following the production of a large, superficial defect of the skin as a result of a burn, there develops a granulation tissue, but months may pass before the wound surface is covered over with epithelium from the edges and the process thereby brought to a close.

FIG. 231.—Necrosis of fifteen years' duration in the lower part of the diaphysis of the femur. *a*, Sequestrum; *b*, *c*, edges of the opening in the thickened bone (alcoholic preparation). Reduced one-third.

A further cause of chronic

inflammation is found in *constantly repeated injury by external influence*

For example, the frequently repeated inhalation of dust may cause chronic inflammation of the lungs; repeated rubbing of the skin may cause a chronic inflammation of the part affected; pathological alterations of the stomach contents may cause chronic inflammation of the stomach. In the canals of the body in which *concretions* may form, the latter may give rise to lasting tissue-lesions.

When there exist in a tissue *unfavorable nutritive conditions*—i.e., marked congestion—these may enable slight external influences, that under normal conditions either produce no inflammation at all or one soon subsiding, to set up ulcerative processes showing no tendency to heal. In this manner, for example, chronic ulcers of the leg may arise.

A very frequent cause of chronic inflammation is furnished by *infections*, particularly those caused by *bacteria* and *moulds*, which multiply in the body and thus constantly give rise to new inflammatory irritation. The inflammations which they cause are distinguished from others chiefly by the fact that they lead to connective-tissue proliferations (*infectious granulation tumors*), and that they usually show a *progressive character*, and form metastases through the lymph- and blood-vessels.

Finally, *chronic intoxications* form a last cause. These affect chiefly the kidneys and the liver, and may be attributed either to the continued introduction into the organism through the gastro-intestinal tract, lungs, or skin

FIG. 222.—Changes in the pleura and lung after a p[...] lent pleuritis lasting six months (alcohol, orcein). [...] Thickened lung tissue with gland-like alveoli, and ela[...] fibres in the newly formed connective tissue; *b*, th[...] ened pleura; *c*, newly formed connective tissue wit[...] elastic fibres; *d*, granulation tissue covered with pus [...] elastic limiting membrane of the pleura; *f*, elastic fib[...] × 46.

of substances harmful to the organs directly concerned or to others; or injurious substances may be produced within the body itself, through disturbances of the processes of metabolism, thus giving rise to a *chronic autointoxication.*

The **forms of chronic inflammation** are determined partly by their fundamental causes, partly by the character of the affected tissue.

Chronic inflammations characterized especially by **hyperplastic formations of connective tissue** are found especially in the serous membranes, lungs, and skin, but may occur also in other tissues. Chronic pleuritis, caused by exudates which are with difficulty absorbable, or by chronic infections, lead to extensive *scar-like thickenings of the pleura* (Fig. 232, *b, c*), the new-formation of tissue occurring in part upon the pleura (*c*) and in part within it (*b*). Moreover, *induration of the lung* (*a*) may follow various *infectious inflammations,* or may be caused by the continued *inhalation of stone dust,* in the latter case being characterized by the formation of fibroid nodules (Fig. 233, *a*), in part also by diffuse induration (*c*).

FIG. 233.—Section of a stonecutter's lung with fibroid nodules (alcohol, picrocarmine). *a*, Group of fibroid nodules; *b*, normal lung tissue; *c*, thickened lung tissue still containing bronchi, vessels, and a few alveoli. × 9.

Continued irritation in the neighborhood of the orifices of the urogenital apparatus, as through the discharge of irritating secretions (chronic gonorrhœa), leads frequently to the formation of *pointed condylomata* (*condylomata acuminata*)—i.e., to a hyperplasia of the papillæ and epithelium, in which the inflamed and infiltrated papillæ grow out with their vessels (Fig. 234, *a, b*) and frequently divide into branches.

FIG. 234.—Condyloma acuminatum (injected preparation). *a*, Enlarged branching papillæ; *b*, epidermis. × 30.

Frequently repeated or continued slight inflammations of the skin and subcutaneous tissue, due to mechanical lesions, parasites, or any other continued irritation, may also, if they reach a considerable extent, give rise to a diffuse hyperplasia of connective tissue, which is known as *elephantiasis.*

Inflammatory proliferations of the periosteum and bone-marrow, which give rise to *pathological new-formations of bone* or a *hyperostosis* (Fig. 235), may be caused both by non-specific irritations—for example, by inflammations which run their course in the neighborhood of chronic ulcers—as well as by specific infections—for example, syphilis or tuberculosis.

Chronic catarrhs of the mucous membranes are sometimes caused specific infection (gonorrhœa, tuberculosis), sometimes by non-spe injuries (concretions, pathological changes in the gastric or intest contents), and sometimes by continued disturbances of circulation (gestion).

Chronic abscesses arise usually from acute abscesses, and have same etiology as the latter; but may also develop more gradually and then caused by special infections, most frequently tuberculosis and actinomycosis. They are usually limited externally by a connective-tissue membrane covered with granulation tissue, and may increase in size partly through the secretion of pus from the abscess-wall, and partly through the destruction of the wall and the neighboring tissue. Progressive enlargement toward the deep-lying parts leads to the formation of **burrowing or congestive abscesses.** Their increase in size is always to be ascribed to the persistence of the infection. Perforation into neighboring tissues leads accordingly, also, to new infective inflammations.

The tuberculous and actinomycotic forms of chronic abscesses are distinguished from other forms partly by the specific characteristics of the pus and partly by the peculiar structure of the abscess-membrane (see Tuberculosis and Actinomycosis, Chapter X.).

Chronic ulcers are caused chiefly by specific infections (tuberculosis, syphilis, glanders), but non-specific injurious agents may lead to chronic ulcerative processes in tissues which are especially susceptible to such changes. Thus chronic congestion in the vessels of the leg may have such an effect that ulcers arising through any mechanical influence may be prevented from healing under the unusual conditions in which the leg finds itself. Likewise peculiar qualities of the stomach contents may hinder the healing of an ulcer of the stomach. If healing begins at one edge of an ulcer while the ulceration advances at other parts, there arises the form of ulcer known as *serpiginous*. The excessive development of granulation tissue in an ulcer leads to the production of an *ulcus elevatum hypertrophicum;* a dense callous, lardaceous thickening of edge and base gives rise to the form known as *ulcus callosum*, or *indo* or *atonicum*.

FIG. [illegible].—Periosteal hyper of the tibia, at the base of a c ulcer of the leg. Reduced fifths.

Chronic proliferations of granulation tissue—i.e., *granulations* *persist as such* for a longer or shorter time without becoming changed connective tissue—occur chiefly in various **specific infections**, the known being *tuberculosis, syphilis, leprosy, glanders, rhinoscleroma,* *actinomycosis.* Since the granulations in these infections often

fungoid proliferations and tumor-like formations, they are often also called **fungous granulations** or **caro luxurians** and **infectious granulation tumors** or **granulomata.** All these show certain peculiarities which enable us to recognize, from the structure, origin, and life-history

FIG. 236.—Section through the mucosa of an atrophic large intestine (alcohol, alum-carmine). *a*, Glandular layer decreased to one-half its normal height; *b*, muscularis mucosæ; *c*, submucosa; *d*, muscularis; *e*, total atrophy of the mucosa. × 30.

of the granulation-formation, also its specific etiology (see Chapter X.). It should be noted, however, that the etiology of some of the granulomata developing in the skin is still unknown.

Chronic inflammations in which **atrophy of the specific tissue** is

FIG. 237.—Induration and atrophy of the renal tissue in chronic nephritis (alcohol, alum-carmine). *a*, Thickened and fibrous capsule of Bowman; *b*, normal glomerular vessels; *c*, glomerulus whose vascular loops are in part impermeable and homogeneous, and the epithelium for the greater part lost; *d*, completely obliterated glomerulus; *e*, homogeneous masses of coagulation, arising from exudate and desquamated epithelium, and studded with nuclei; *f*, desquamated glomerular epithelium; *g*, capsular epithelium; *h*, collapsed urinary tubule with atrophic epithelium; *i*, collapsed tubule without epithelium; *k*, hyperplastic connective-tissue stroma; *l*, cellular foci; *m*, normal, somewhat dilated tubules; *n*, afferent vessel; *o*, vein. × 250.

associated with **hyperplasia of the connective tissue,** occur particularly in the mucous membrane of the gastro-intestinal tract, and in the kidneys and liver.

In the **intestinal canal** the cause may lie in specific (dysentery) as well as in non-specific irritations; the latter being dependent upon some abnormal property of the contents of the canal. The epithelial elements may undergo necrosis in association with persistent desquamation, the connective tissue being unaffected; or they may necrose and disintegrate at the same time with the connective tissue upon which they rest. The final result is a mucous membrane (Fig. 236) which either contains no glands (*e*) or only rudimentary ones (*a*).

In the **liver** and **kidneys** the chronic inflammations which lead to atrophy and induration, and whose final results are known as **cirrhosis of the liver** and **indurated contracted kidney**, are hæmatogenous diseases, in so far as they do not depend upon disturbances in the efferent

FIG. 238.—Connective-tissue hyperplasia and proliferation of bile-ducts in chronic hepatitis (alcohol, hæmatoxylin). a, a_1, Liver-lobules; *b*, hyperplastic periportal connective tissue; *c*, old bile-ducts; *d*, newly formed bile-ducts; *e*, foci of small-celled infiltration. × 55.

passages (obstruction, inflammation of pelvis of kidney, formation of concretions), and are caused partly by *infections* and partly by *intoxications*. They may begin either as acute inflammations or more insidiously, and are characterized by atrophy and degeneration of the glandular tissue (Fig. 237, *h*, *i*), hyperplasia of the connective tissue (Fig. 237, *a*, *k*, and Fig. 238, *b*), through cellular infiltration, formation of granulation tissue (Fig. 237, *l*, and Fig. 238, *e*), through obliteration of old vessels (Fig. 237, *c*, *d*), and through the formation of new vessels. In the liver there occurs also very frequently a formation of new bile-ducts (Fig. 238, *d*), which, however, for the greater part do not functionate.

CHAPTER VIII.

Tumors.

I. General Considerations.

§ 99. A **neoplasm**, or **autonomous new-growth, atypical blastoma** or **tumor** in the narrower sense, is a *new-formation of tissue, apparently arising and growing independently, having an atypical structure, inserted uselessly into the organism, possessing no function of service to the body, and showing no typical termination to its growth.* The atypical character of the structure of a tumor is shown in its external appearance as well as in its internal organization in that a true tumor departs more or less in structure from that of a normal organ. When this departure is but slight, the structure of the tumor approaches closely to that of the tissue-hypertrophies; and there occur cases in which the difference in structure is so little that it becomes very difficult to decide whether an excessive new-growth of tissue is to be classed as a tumor or a hypertrophy.

Tumors may develop in any tissue of the body which is capable of growth, and **arise through the proliferation of the tissue-cells,** associated with a **new-formation of blood-vessels.** Not infrequently there occurs also an *emigration of leucocytes and lymphocytes* into the tumor, and exudative processes and inflammatory tissue-proliferations may take place in its neighborhood, but these phenomena form no essential part of the development of the tumor.

The processes of cell-division and new-formation of blood-vessels are the same as those described in §§ 80 and 82—i.e., the division of the cells takes place by karyomitosis, and the new vessels are formed from buds given off by the proliferating cells of the walls of old vessels. The mitoses are for the greater part typical (Fig. 239, *b*), but there are also found relatively often atypical forms, such as asymmetrical divisions, nuclear figures with abnormally large chromatin masses (so-called giant mitoses), pluripolar mitoses, and forms of nuclear fragmentation, and also direct segmentation.

In their fully developed condition tumors are for the greater part well defined *from the surrounding tissues,* but in some cases *they may pass into the neighboring tissue without any sharply defined border of transition.* Further, *an entire organ may become transformed into a tumor, or large portions of tissue not sharply outlined from their surroundings may take on the character of a tumor.* Through the disintegration of tumor tissue there very frequently arise *ulcers.*

The difference between the structure of a tumor and that of normal tissue is usually recognizable even macroscopically, but there are also tumors which so closely resemble the parent tissue from which they arise that the difference can be made out only through a more careful examination.

The *circumscribed tumors* are usually *nodular* (Figs. 240, *d;* 242, *d, e;* 243, *a*). The size of the single nodules varies, according to the kind of

tumor and the stage of development at the time of examination, fro[m] smallest visible miliary and submiliary nodules to masses weighing [illegible] twenty kilograms or more. When situated upon the surface of an [illegible] nodular tumors not infrequently take on the form of a sponge (Fig. [illegible] *d*) or of a polyp, and are accordingly designated *fungoid* or *polyp[oid tu]mors*. When a new-growth on the surface of a mucous membrane [illegible] skin leads to an enlargement and branching of the papillæ there pr[illegible] or if new papillæ are formed, there arise *warty*, *verrucose*, and *pap[illary] tumors* or *papillomata* (Fig. 241). A further development of the pap[illary] structure may lead to a *dendritic branching* and the formation of a [*cauli*]*flower* mass.

Tumors usually develop from small beginnings; only rarely do [they] arise from centres extending diffusely throughout an entire organ. [illegible]

FIG. 240.—Tissue from a carcinoma of the breast, containing numerous division-figures in differe[nt] [illegible] [illegible] *a*, Stroma; *b*, epithelial plugs. × 300.

growth may be either rapid or slow, and with occasional periods o[f] [quies]cence. Their growth may be suspended for years, and then sud[denly] again they become active.

The **structure of the tumor** is *determined by the parent tissu[e]* which gives it origin; and although the true tumors always show [illegible] *[illegible] character*, they yet retain certain characteristics of the p[arent] tissue.

According to the [illegible] and genesis tumors may be divide[d] [illegible] *connective-tissue tumors*; 2. *epithelial tumors*; 3. [illegible] [illegible] [illegible] there are many [illegible] [illegible] which, according to the point of view, may be classed [illegible] [illegible]

The **connective-tissue tumors**, or the **tumors arising from the [sup]porting-tissue substances**, and which are often called [illegible] [illegible] [illegible] correspond in part to matur[e] [illegible] [illegible] mesoderm, and [illegible] [illegible] mesodermic connective tissues [illegible]

are also included in this group those tumors arising from the specific elements of the nervous system, the glia-cells and ganglion-cells, and also the muscle-tumors, since these in their structure resemble the connective-tissue tumors much more than they do the epithelial.

FIG. 240.—Fungoid carcinoma of the endometrium of the posterior wall of the uterus. *a*, Body of the uterus; *b*, cervix; *c*, vagina; *d*, tumor. Two-thirds natural size.

The differences in the types of the connective-tissue tumors are essentially dependent upon the character of the ground-substance, and in part also upon the cells. When the tumors are very rich in cells and the ground-substance but slightly developed, they acquire a soft consistency and are classed with the *sarcomata.* Very soft forms are designated as *medullary* or *fungi medullares.* Through the combination of different forms of connective tissue there arise *mixed connective-tissue tumors.*

The **epithelial tumors** are composed of cells derived from *surface epithelium* or from *gland-cells,* and also of *vascular connective tissue*—which forms a supporting framework in the spaces of which the cells arising from the proliferation of surface epithelium or gland-cells lie in definite groups. Inasmuch as this arrangement gives to the tumors a structure suggesting that of a gland, they are often also called *organoid tumors,* in contradistinction to the histoid connective-tissue tumors. It should be noted, however, that there are also included in the connective-tissue group of tumors certain varieties (endotheliomata) which have an organoid structure.

The cells which give the epithelial tumors their especial character arise either from the ectoderm or entoderm, and from the glands developing from the same, or finally from the mesodermal epithelium of the pericardium, and of the pleural and peritoneal cavities, or of the glands arising from this layer (kidneys, sexual glands, adrenals). Tumors having the last-named origin often show more or less distinctly the especial character of the parent tissue from which they arise.

FIG. 241.—Papillary adenoma of rectum. Natural size.

Very soft cellular epithelial tumors are also designated *medullary.*

Combinations of epithelial proliferations with proliferations of the connective tissue, which exceed the ordinary amount of supporting tissue or bear a sarcomatous character, lead to the formation of *epithelial mixed tumors.*

The **teratoid tumors and cysts** form a group which is especially characterized on the one hand by the fact that they contain the most varied kinds of tissue which may be derived from all three germ-layers (*teratoid mixed tumors*), and on the other hand by the presence of tissue formations in regions where they do not normally occur. Tumors, therefore, which according to their structure may be placed in one of the other groups, may be considered as teratomata on account of their situation. Further, there are also included in the group of teratoid tumors certain formations which according to their structure, origin, and physiological relations ought not to be classed with the tumors.

Tumors usually develop **singly**; but it also happens that within a certain tissue system there may appear either coincidently or in succession a **great number of tumors of the same kind,** so that it must be assumed that the conditions requisite for the development of these tumors were present in different parts of the system affected. At times there develop in different organs of the *same* individual two *entirely different varieties of tumors,* which stand in no relation to each other, and whose coincident appearance is purely accidental.

The exact determination of what should be included under the term **tumor** is hardly possible; and consequently the designation tumor is applied to many different formations which, according to their etiology, genesis, and life-characteristics, have not the same significance. The idea of tumor is, therefore, very differently conceived by different authors. I regard it as advisable, and also as based upon the life-characteristics of the tissue-formations which we are about to consider, to exclude in the first place from the class of tumors all hyperplastic proliferations, and further all retention-cysts which arise purely through the retention of secretions and show no independent new-formation of tissue. Further, according to my view, *there should be separated from the true tumors all proliferations of tissue due to the presence of parasites* or *to infection,* particularly the infectious granulomata which occur in tuberculosis, syphilis, leprosy, etc. Should it be proved—which so far has not been done—that some of the new-growths now included with the true tumors are caused by infection, they should also be excluded from the category of true tumors.

The above **classification of tumors** is based essentially upon their histological character and histogenesis. They may of course be classified according to other points of view. *Lubarsch* has offered the following classification with reference to the growth and behavior of the tumor: (1) Tumors which differ from the parent tissue in the arrangement of their elements, but for the chief part present no recognizable increase or at most only a transitory growth (various teratoid new-growths, misplaced tissue anlage, congenital nævi, many adenomata, myomata, fibromata, lipomata, chondromata, and osteomata); (2) tumors which show a certain autonomy and independence in their structure, but yet on the whole obey the normal laws of life in that they always respect the physiological tissue boundaries (myomata, adenomata, angiomata, lipomata); (3) tumors which are wholly emancipated from the physiological laws of life and rule in the tissues in total lawlessness of growth (carcinoma, sarcoma).

The **atypical structure of tumors** is not given so much prominence by all authors as has been done above. This is particularly true with reference to those tumors which are similar in structure to the parent tissue from which they arise, and which are accordingly designated *homoplastic tumors.* It should be noted, however, that even in these tumors, in so far as they represent true neoplasms (chondroma, osteoma, fibroma, etc.), there occur in general, in the histological structure, coarser organization, and external form, pronounced departures from the normal. Tumor-like congenital tissue-hypertrophies (for example, many osteomata), as well as hyperplastic new-formations of tissue resulting from inflammatory processes, must be separated from the true tumors.

Tumors are in no sense useful to the organism as many tissue-hypertrophies may be. Tumor-tissue does not possess the specific activity of that tissue from which

it springs, so that tumors can in no way be regarded as useful new-formations of tissue. It happens, indeed, that in certain tumors there occur **processes** of **secretion** which correspond to normal secretions—thus, epithelial tumors may produce mucous or horny or colloid material (thyroid tumors), or bile-pigment (liver-tumors), even in metastatic nodules—but from these facts we can conclude only that, in many tumors which do not differ too greatly in structure from the parent tissue, the cells may retain, to a certain degree, for a number of generations, the functional capacities of the parent tissue. There is, however, no basis for believing that new useful tissue is formed as in the case of hypertrophy from increased labor; the products are for the chief part of no use to the body, and though perhaps in especial cases the iodine-containing colloid produced by malignant tumors of the thyroid may be made use of, such a function must surely be of much less value than that of the normal tissue.

The tumors arising from the mesodermal epithelium of the serous membranes or of the glands arising from these are included in the **group of epithelial tumors.** This is justified by the fact that such tumors correspond in their structure and clinical behavior to the epithelial tumors of the ecto- and entoderm. I have also considered the question whether it would not be advisable (as *Hansemann* has proposed) to class also among the epithelial tumors—i.e., the adenomata and carcinomata—those tumors which have a framework of connective tissue, the spaces of which are filled, in a manner suggesting epithelial tissues, with cell nests arising from the proliferating endothelium of the blood- and lymph-vessels. Aside from the similarity in the structure of these tumors with the ordinary adenomata and carcinomata, there may be taken in favor of this view the fact that from the anatomical side the endothelium of the blood- and lymph-vessels is often designated as mesodermal epithelium. Against such a grouping of the endothelial with the epithelial tumors may be urged the facts that, aside from the general acceptance of the term endothelioma, the behavior of the endothelium of the blood- and lymph-vessels under pathological conditions is very different from that of epithelium, and that in many tumors it is impossible to separate the products of the growth of the endothelium of the blood- and lymph-vessels from the products of proliferation of connective-tissue cells.

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See also §§ 100 and 101.

§ 100. The **etiology of tumors** is by no means uniform, and very often cannot be determined with certainty. In the majority of cases, however, the *conditions*, at least, under which the new-growth appeared can be assigned and we may accordingly establish different groups of tumors. *Infection* is indeed very frequently advanced as a cause of tumors, but such etiology has not in any case been demonstrated beyond doubt.

As the first group of tumors, according to etiology, may be taken *those arising from especial congenital anlage*, so that we may in a certain sense regard them as *local malformations of tissue*. They develop either in uterine life, and are present at birth, or later in extra-uterine life, during the period of growth or even later, in which case trauma not infrequently gives the immediate occasion for the beginning of the development of the tumor from the preëxisting anlage.

To this group belong in the first place many osteomata, chondromata, angiomata, gliomata, fibromata (of the nerves and skin), sarcomata and adenomata. Further, many teratoid tumors and cysts are also to be included in this group, inasmuch as they represent in part either remains of fœtal structures, transpositions or monogerminal inclusions of embryonic tissue, implantations of rudimentary portions of a twin embryo (bigerminal implantations), or probably also the results of disturbances of the earliest stages of the development of the ovum.

A *second group develops after traumatic injuries of the tissues*; and it has been reckoned that in about seven to fourteen per cent of cases a traumatic origin can be assigned; particularly in the case of sarcoma, carcinoma, and osteoma. The causes of the tumor-formation may be a single injury, a stab, a blow, crushing, fracture, etc., as well as repeated mechanical irritation, such as rubbing, scratching, etc.

In a third group the development of the tumor follows inflammation, particularly the formation of granulation tissue with subsequent cicatrization. The inflammation and ulceration may be caused by non-specific as well as by specific injurious agents. For example, cancer of the gall-bladder (Fig. 242, *d*, *e*) almost invariably develops only in gall-bladders which contain stones, and are consequently the seat of chronic inflammation. In the stomach, cancer may develop in the edge of an ulcer or in the resulting scar and also in a mucous membrane which has suffered severe changes as the result of previous inflammation. In the external skin and also in the mucous membranes of the pharynx and larynx cancers occasionally

arise in the base of a tuberculous or syphilitic granuloma or in the scar of such a process.

In a fourth group the development of the tumors appears to owe its origin

FIG. 242.—Primary carcinoma of the gall-bladder enclosing an impacted gall-stone. Frontal section through the gall-bladder and liver. *a*, Liver; *b*, duodenum; *c*, gall-stone; *d*, wall of the carcinomatous gall-bladder; *e*, cancerous infiltration of the neighboring liver tissue; *f*, portion of duodenum which is infiltrated with cancer and adherent to the gall-bladder tumor. Natural size.

to an unequal atrophy of the elements which make up a tissue, so that certain hindrances to growth are removed or lessened. Not mechanical resistance alone, but influences dependent upon the chemical conditions of the tissue, should be considered in this connection. Here belong especially certain *epithelial proliferations* (*cancers*) which develop in old age, or in organs which after a period of increased activity become atrophic. In this way, for example, the development of cancer of the skin may be explained on the ground that the connective tissue of the skin undergoes a certain retrogression leading to a relaxation of its structure, while the epithelium is still possessed of its full power of proliferation. At the same time the chemical composition of the connective tissue may be altered.

It cannot be doubted that the **etiology of tumors** is not always the same, as is shown by the variety of conditions under which they arise.

It is difficult to say what is the nature of the influence which excites the cells to the *production of an atypical tissue.* We are at first inclined to think of the same causes which underlie hypertrophy and regeneration of tissue, also, on the one hand, of especial congenital anlage or of stimuli which increase the formative activity of the cells,

and on the other hand, of a lessening or removal of hindrances to growth. But it still remains a problem why there should not be formed typical tissues which would so fit into the organization of the body that they would be of service to the latter. In the attempt to explain this phenomenon, which is at the same time associated with an increase in the vital and reproductive capacities of the cells, even under pathological conditions (metastasis of the cells through the blood- and lymph-vessels), many writers have sought and would recognize as the cause the presence of *parasites* (see Etiology of Carcinoma); but our present knowledge does not in any way justify us in attributing the development of true tumors, of autonomous new-growths, to the influence of parasites. On the contrary, the development and life-history of tumors, and in particular the formation of metastases, which without doubt arise through the multiplication of living tumor-cells transported in the lymph- or blood-stream, speak against the hypothesis of the parasitic nature of tumors.

Cohnheim advanced the theory that all true tumors arose from especial tumor-anlage which had their origin in the persistence of foci of embryonal tissue. Neither the results of clinical observation nor of the anatomical investigation of the tissues speak in favor of such a theory.

Ribbert is of the opinion that the cause of the pathological proliferation which leads to tumor-formation is to be found particularly in a separation of cells or cell-groups from their organic relations, such a separation occurring either as the result of intra-uterine disturbances of development or later under the influence of external agencies. Nevertheless, such transplantations or separations of cell-groups take place very frequently in intra-uterine life, or after trauma, after ulceration, in scars and in infectious granulomata, without any subsequent development of a tumor. These *transplantations of tissue constitute only one of the predisposing causes of tumor-formation*, but some other factor is necessary to excite the atypical progressive tissue-proliferation—i.e., the development of the tumor. The *development of a tumor is, therefore, in no wise dependent upon a transplantation of tissue; rather does the tumor-proliferation take its origin in cells which are normally situated;* and this may be actually demonstrated, particularly in the case of epithelial tumors.

Beard holds the view that tumors, in particular the carcinomata, arise from sexual cells which, during the development of the body, have been displaced between the somatic cells and are there preserved.

Our knowledge of the causes of tumor-development at the present time may be summed up as follows: Inherited and acquired conditions of certain cells and cell-groups, which assert themselves in a tendency to increased formative activity with the production of atypical tissue, lead to the formation of tumors. In many cases this proliferation is prepared for, favored, and excited by the transplantation of cells and cell-groups, but often also through changes in the neighborhood of the cells concerned. No general scheme applicable to the development of all tumors can be given. On the contrary, the conditions vary not only with the different forms of tumors, but also with the individual cases of the same tumor-type. Moreover, it should not be forgotten that the formations which we class as tumors do not all possess the same significance, and that many of the same ought more properly to be classed with other phenomena of growth (malformations).

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See also § 99.

§ 101. When once a **tumor** has arisen in any tissue and has reached a certain stage of development it **may become quiescent in growth,** and remain for a life-time without undergoing further change. This is true particularly of those tumors which according to their origin are regarded as *local tissue-malformations;* but tumors which develop first in later life may also come to a standstill after attaining a certain size.

The **growth of a tumor takes place independently,** and in many cases continues even until death occurs.

From the surrounding tissues the tumor acquires both its blood-vessels and thereby its food material, but may besides grow independently—i.e., through an increase of the cells which form the elements of the tumor. In many cases the tumor increases in size essentially through an

interstitial expansive growth, and the neighboring tissue is only crowded or pushed aside. In other cases the **tumor tissue grows by infiltration** and *forces its way into the intercellular spaces of the neighboring tissue*, so that new areas of tissue are thus brought under the influence of the tumor. In this way the cells of the newly invaded tissue are often excited to proliferation, so that an enlargement of the tumor takes place through an *appositional growth*, in which both the cells of the original tumor and of the surrounding tissue take part.

The characteristic feature of **growth by infiltration** consists in the *involvement of the tissues of the organ* which lie in the neighborhood of the primary tumor. Further, the *tissue of neighboring organs* (Fig. 242, *e*, *f*)

FIG. 243.—Section through a primary cancer of the liver (*a*), with multiple metastases (*b*) within the liver itself. Three-sevenths natural size.

may become involved by the tumor through its spread by *contiguity*. If *tumor-cells gain entrance into the great body-cavities they may spread over the serous surfaces and lead to the development of tumors.*

If, in the process of infiltration, a tumor *gains entrance into a lymph- or blood-vessel*—an event which in particular is always likely to occur in the case of the tumors called carcinoma and sarcoma—and *if living tumor-cells capable of proliferation* are transported through the lymph- or blood-vessels, there often arise **tumor-metastases**—i.e., a development of **daughter-tumors** which are not directly connected with the primary tumor. The daughter-tumors may at first develop in the organ primarily affected (Fig. 243, *b*), but usually soon involve other organs as well; in the case of rupture into the lymph-vessels the *lymph-glands* are first affected; in rupture into the blood-vessels, *those organs to which the blood carries the living cells.* The direction of the transportation is usually that of the lymph- and blood-stream, but retrograde transportation not infrequently occurs, particularly in the lymph-vessels, the lumina of which are easily obstructed by tumors.

The development of daughter-tumors takes place in all cases from transported cells. In the event of **metastasis by the lymph-vessels** the affected lymph-vessels (Fig. 244, *a*) are first filled with cells, which

develop from the transported tumor-cells. Later there follow a proliferation and new-formation of blood-vessels on the part of the neighboring tissue, and as a result of these processes there develop larger or

FIG. 244.—Periglandular lymph-vessel (in the axillary region) filled with cancer-cells arising from a primary carcinoma of the mammary gland (Müller's fluid, hæmatoxylin). *a*, Cancer-cells; *b*, wall of lymph-vessel. × 300.

smaller *nodules*. It also not infrequently happens that the *lymph-vessels are more uniformly distended by the growth* (Fig. 244, *a*), without any real formation of nodules, or at least only small swellings develop along the course of the lymph-vessels. In the event of metastasis into *lymph-glands*

FIG. 245.—Metastatic development of cancer in the branches of the portal vein and liver-capillaries (Müller's fluid, hæmatoxylin, and eosin). *a*, Liver tissue; *b*, plugs of cancer-cells in the portal vein; *c*, cancer-cells in the capillaries. × 100.

the latter become swollen, forming *nodules* of smaller or larger size, in which the tissue of the lymph-gland is gradually replaced by tumor tissue.

In the case of **metastasis through the blood-vessels** the first development of the secondary tumor begins with the tumor-cells forming the em-

bolus in artery, capillary, or vein, and under certain conditions the vessels (Figs. 245, *b*, *c*; 246, *b*, *c*) may be filled and greatly dilated by the proliferating tumor-cells. The tissue in which the tumor-embolus develops may at first remain passive, and the specific tissue-elements—gland-cells (Fig. 246, *d*) and muscle-cells—may vanish as the result of increasing atrophy. Later, the blood-vessels and connective tissue take part in the development of the secondary tumor.

In the further course of its development the secondary nodule is usually sharply circumscribed from its surroundings and grows by expansion. It, however, not infrequently happens that, at least in places,

FIG. 246.—Metastatic sarcoma of the liver from a primary sarcoma of the parotid (Flemming's solution, safranin, picric acid). *a*, Liver-rods; *b*, sarcoma tissue developing within the vessels; *c*, isolated tumor-cells in the liver-capillaries; *d*, liver-cells which have undergone atrophy and fatty degeneration. × 150.

the infiltrative growth persists, and under certain conditions widespread diffuse tumors develop, particularly in the bone-marrow and in the liver (Fig. 246).

The number of lymphogenous and hæmatogenous metastases varies greatly in different cases. At one time the metastases may be confined to one organ, at other times they may be scattered throughout several. In rare cases cells of the original tumor may be spread through almost the entire body, so that in the most diverse organs—glands, muscles, skin, etc.—larger and smaller nodules may appear in quick succession. This phenomenon is possible when tumor-nodules situated in the lung, pleura, or bronchial glands break into a pulmonary vein, or when the tumor cells pass through the lungs.

If a living bit of tumor (carcinoma, sarcoma) capable of forming metastases is transplanted from one animal into the tissues of another animal of the *same species*, it sometimes happens that it will develop in the second animal. There may take place, therefore, a *metastasis from one animal to another*. In man, tumor particles may in a similar manner be transplanted during operations from one part of the body to another and there contine to grow (implantation metastasis).

Side by side with the progressive proliferation of tissue there very frequently occur in tumors **retrogressive changes**, particularly in rapidly growing and infiltrating cellular tumors, in which fatty and mucous degeneration, necrobiotic processes, and hæmorrhages may take

place to a marked degree, so that there not infrequently results a total *destruction of the tumor tissues.* This rapid disintegration of the tumor is in part due to the fact that in carcinomata the epithelial proliferation to a very great extent grows into the blood-vessels and so obstructs them. If the cells are badly nourished they may undergo necrosis and become dissolved through the action of proteolytic ferments. In the case of nodular tumors the destruction of the tumor-cells, when followed by a resorption of the products of degeneration, leads to *shrinking* and to the formation of *cicatricial contractions.* Very often *degeneration-cysts* and *ulcers* may be thus formed; and particularly in the case of carcinomatous tumors of the mucous membranes the parts of the tumor growing up above the surface very often for the greater part undergo disintegration. In slowly growing tumors of ~~hard consistency extensive retrograde~~ changes do not usually occur.

The necrosis and disintegration of the tissues of the tumor only very rarely terminate in a **cure.** This event is most likely to happen when a polypoid new-growth becomes totally necrotic (for example, as a result of twisting or tearing of its pedicle) and is thrown off. In the majority of the tumors showing a tendency to retrogressive changes and disintegration, while the older portions are dying the growth constantly advances at the periphery, so that new tissues are being progressively attacked by the tumor.

FIG. 247.—Recurrent sarcoma in the amputation-stump of the femur. *a*, Fungoid tumor arising from the bone-marrow; *b*, periosteal nodules; *c*, metastasis. One-half natural size.

If the **tumor is extirpated,** there may result a **cure** when all of the growth has been removed or destroyed. This is most easily accomplished in the case of slowly growing and sharply circumscribed tumors which increase by expansion. In the case of infiltrating tumors it is very difficult to determine the boundary of the tumor-growth, since this may often extend far beyond the point where any macroscopic change in the tissue is apparent. Consequently, in such cases there takes place, sooner or later, in the operation scar a **recurrence** (Fig. 247, *a*) which arises from portions of the tumor remaining in the tissues. Such recurrences behave exactly like the primary tumor, and may also form metastases (Fig. 247, *c*). In those cases in which recurrence in the scar following operation is long delayed, it is possible that this circumstance depends upon the fact that in the affected area the *conditions favoring tumor development again occur.*

According to their clinical and anatomical characteristics **tumors** may be classed as **benign** and **malignant.** As *benign tumors* are generally regarded those *which grow slowly and by expansion and do not form metastases;* as *malignant, those which show a complete emancipation from the*

normal laws of proliferation, grow quickly and by infiltration, easily undergo degenerative changes and form metastases.

The **malignant tumors**, on the whole, coincide with those tumor forms which are known as *carcinoma* and *sarcoma*. It must, however, be borne in mind that the malignancy of a tumor depends not only upon its character, but also upon its location. A benign tumor takes on a malignant character as soon as its presence interferes with the functions of vital organs. Hence every tumor of the brain or meninges becomes a dangerous affection at the moment when it gives rise to disturbances of the cerebral functions. Under certain conditions such benign tumors as fibromata of the uterus become destructive growths as soon as they reach such a size as to displace and compress the neighboring organs.

After a tumor has existed for a certain period there results very frequently a marked lowering of the general nutrition, a marasmus, which is usually designated **tumor-cachexia.** This occurs chiefly in association with the malignant growths known as cancer and sarcoma; and may depend, in part at least, upon the great demands made upon the food supply by the rapid growth of the tumor, particularly in the case of formation of metastases. A still more important cause may lie in the fact that the tumor may interfere with the taking-in of food. In cancer of the œsophagus, stomach, and intestine the function of the affected organ is greatly interfered with, and the assimilation of food may be entirely prevented or nearly so. Further, it should be borne in mind that through the degeneration of the tumor and the continuous secretion from the resulting ulcers large amounts of albuminous material may often be lost from the body; and that through putrid decomposition there may arise substances which, when absorbed, may act injuriously upon the organism. Finally, the pain which is often felt in a tumor may rob the patient of his sleep. Whether the tumor itself, in certain cases, produces substances harmful to the organism is yet unknown, but is, however, not improbable.

Metastases occasionally occur with **benign tumors,** chondromata, myomata, and adenomata. Of these, the metastases in the bones of thyroid tumors are of special importance; they occur when no carcinomatous proliferation can be demonstrated in the thyroid, so that it would seem probable that under certain conditions even the cells of a normal or hypertrophic tissue may be transported into the bone-marrow and there proliferate.

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See also § 125.

II. The Different Forms of Tumors.

I. Tumors Derived from Connective Tissue or the Supporting Framework.

(*a*) *Fibroma.*

§ 102. A **fibroma** is a tumor composed of *fibrous connective tissue*. It occurs most frequently in the form of *nodules*, which are sharply circumscribed from the surrounding tissues, and usually involve but a portion of the affected organ. Very rarely an entire organ (ovary) may become changed into a single tumor-mass. On a free epithelial surface and on mucous membranes a fibroma may appear in the form of a *papilloma* or a *polyp*.

FIG. 248.—Hard fibroma from lobe of the ear (alcohol, hæmatoxylin). *a*, Longitudinal section; *b*, transverse section of bundles of fibres. × 400.

According to the character of the connective tissue of which it is composed, the consistency of a fibroma may vary greatly. Often it is *hard* and *tough*, creaking under the knife (*desmoid*), and showing on its cut surface a white, tendon-like, shining tissue; but in other cases the growth may be soft, flaccid, the cut surface being more uniformly grayish-white and somewhat translucent. In still other cases the individual strands of connective tissue are indeed white and shining, but the tumor as a whole has a looser structure and is correspondingly flaccid.

Between the hard and soft growths there exist all possible transition-forms, and even in one tumor different parts may possess different characteristics. Under the microscope the hard kinds appear to be composed chiefly of thick bundles of coarse fibres (Fig. 248, *a*, *b*), in which lie scattered a larger or smaller number of cells. In the softer forms the bundles of fibres are more delicate

FIG. 249.—Section of an œdematous fibroma of the uterus (osmic acid, glycerin). *a*, Closely lying fibres; *b*, fibres pressed apart by fluid; *c*, spindle-shaped cells; *d*, swollen round cells; *e*, blood-vessel. × 200.

(Fig. 249, *a*). If as a result of venous congestion or other cause a clear fluid collects between the fibrillæ, there is formed an *œdematous fibroma*, whose bundles of fibres (Fig. 249, *b*) are pressed apart by the fluid, the tissue becoming softer and more moist and translucent, and finally resembling the tissue of the umbilical cord.

The *soft forms of fibroma*, which present a partly translucent, grayish-white cut surface, are usually very rich in cells; so that it is possible by teasing to isolate numerous slender spindle-shaped cells (nuclei with

FIG. 250.—Fibroma pericanaliculare mammæ (Müller's fluid, alum carmine, eosin). *a*, Gland-tubules; *b*, newly formed pericanalicular connective tissue rich in cells; *c*, connective tissue poor in cells. × 25.

tails). The intercellular substance is correspondingly less in amount, the fibrillæ more delicate and arranged in finer bundles. Sections through such fibromata, when stained, appear very rich in nuclei (Fig. 250, *b*).

Fibromata develop from proliferating connective-tissue cells, and it is usually possible to find in the tumor certain areas which are richer in cells than the main mass of the tumor tissue, and in which the cells appear not only as small spindle cells, but also in part as round cells, or as short, thick spindles, or even as stellate cells. The transformation of the newly formed cellular tissue into connective tissue takes place in the same way as that described under Hyperplasia of Connective Tissue. A new-formation of elastic fibres is usually wanting, but at times such a new-formation does occur, particularly in the neighborhood of the blood-vessels.

Fibromata may appear in any part of the body which contains any form whatsoever of connective tissue. They occur most frequently, for example, in the nerves, skin, periosteum, fascia, mammæ, and mucous membrane of the nose; more rarely in the ovary, intestinal tract, etc. In the mammary gland the development of the fibroma takes place particularly around the canaliculi (Fig. 250, *b*), so that the latter come to be surrounded by connective tissue rich in cells.

Fibromata do not form metastases, but often occur as multiple tumors, especially in the nerves and skin (see Neurofibroma, § 111). Moreover,

it is not uncommon to see within a tumor several centres of growth—that is, the mass of the tumor is made up of several nodules or bands held together by ordinary connective tissue (Fig. 250, *b*). Fibromata are malignant only through their size and position.

Fibromata may undergo mucous or fatty degeneration or may soften and disintegrate, so that cavities may be formed within them. They may also break through and give rise to ulcers. Their blood-supply varies greatly, at times being scanty, at other times abundant. Occasionally the blood-vessels are ectatic, so that the tissue is interspersed with wide channels and clefts, from which blood escapes when the tumor is examined in a fresh state. In other cases dilated lymph-channels are seen.

Keloid is the designation applied to a hard, nodular, or flat and banded, or stellate growth of the skin, which in its fully developed state consists of dense fibrous tissue without elastic fibres. The direction of the fibres is often at right angles to the surface of the skin, or at least does not accord with that of the normal fibres. It usually develops after injuries or inflammations (*cicatrix-keloid*), but it may also appear without such association (*spontaneous keloid*). The cause of the keloid growth is not known; the tendency to recurrence after removal, the multiple occurrence, and the fact that many cases frequently occur in the same family (Hutchinson) speak in favor of a special predisposition on the part of the skin.

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See also § 112.

(*b*) *Myxoma.*

§ 103. A **myxoma** is a tumor which consists essentially of *mucous tissue*, and is made up of cells and a fluid or gelatinous intercellular substance containing mucin. The cells of the tumor are for the greater part polymorphous, with processes of varying length (Fig. 251) which anastomose with one another (Fig. 252, *a*). The tissue is markedly translucent, soft, and the blood-vessels are easily seen through it. From the cut surface gelatinous masses or a stringy fluid, which swell up in water, may be obtained.

No tumor is ever wholly made up of myxomatous tissue; the latter is usually combined with other forms of tissue, particularly with fibrous connective tissue, fat tissue, cartilage, and sarcomatous tissue. For this reason such tumors are properly designated **fibromyxoma, lipomyxoma** (Fig. 254), **chondromyxoma** (Fig. 257, *c*), and **myxosarcoma** (Fig. 252).

Mucous tissue may develop from fibrous connective tissue through the collection of a mucin-containing fluid between the fibrillæ and the gradual disappearance of the latter. Adipose tissue may pass over into myxomatous tissue through the disappearance of fat from the fat-cells and the appearance of a mucin-containing gelatinous substance between the cells, during which process the fat-drops become broken up into swollen droplets (Fig. 254, *b*, *c*), while the cells themselves become smaller and star-shaped (*d*). Cartilage may also become transformed into mucous tissue through a mucoid degeneration of the basement-substance and a change of form of the cells (Fig. 257, *c*, *d*). Myxosarcomata (Fig. 252) arise either through a local increased activity of cell-proliferation in myxomata or through a collection of mucoid substance between the sarcoma cells.

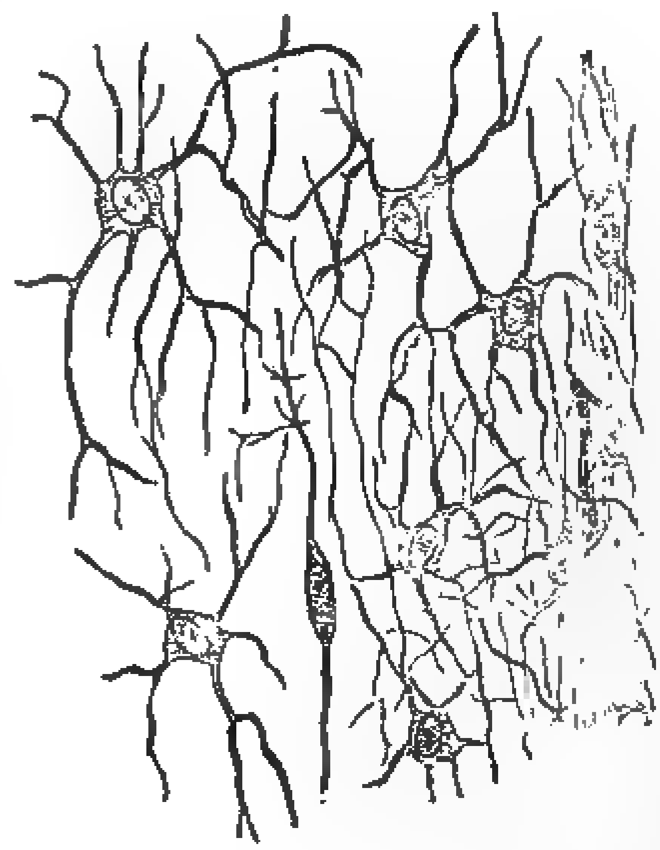

FIG. 251.—Cells from a myxoma of the periosteum of the femur (gold preparation). × 400.

Myxomata, myxofibromata, and myxolipomata develop most frequently in the connective tissue of the periosteum, skin, heart, fascia, and sheaths of the muscles, as well as in the fat tissue of the subcuta-

FIG. 252.—Section of a myxosarcoma (Müller's fluid, carmine, glycerin). *a*, Myxomatous tissue; *b*, strands of cells; *c*, fibrous tissue. × 225.

neous and subserous tissues and of the endosteum. Myxochondromata occur particularly in the parotid, and constitute the most common form of tumor found there.

These forms are all benign tumors, which rarely produce metastases. Myxosarcomata, on the other hand, have the characteristics of sarcomata and may form metastases.

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(*c*) *Lipoma.*

§ 104. A **lipoma** is a tumor consisting of *adipose tissue* (Fig. 253). These tumors are sometimes soft, almost fluctuating, sometimes firm, usually nodular and lobulated, and very often attain a very great size. In structure they are very similar to the subcutaneous adipose tissue—that is, they consist of fat-lobules held together by thick or narrow connective-tissue trabeculæ.

Histologically, the tissue of a lipoma resembles the fat-lobules of the subcutaneous panniculus (Fig. 253), although the tendency to form typical grape-like clusters of fat-cells is wanting. If, as not infrequently happens, mucous tissue is also formed in connection with the fat tissue, or if the latter, following a disappearance of its fat, becomes changed into myxomatous tissue, the tumor is designated a **lipomyxoma** (Fig. 254); if there is an abundance of fibrous tissue present, it is called a **lipofibroma** or **fibrolipoma**.

Fig. 253.—Lipoma of shoulder region, with relatively small fat-cells (Müller's fluid, hæmatoxylin). × 300.

Lipomata develop most commonly from adipose tissue, but may arise also from connective tissue which normally contains no fat. Calcification, necrosis, gangrene, and sloughing are of not infrequent occurrence in lipomata of large size. These tumors do not produce metastases, but are occasionally of multiple occurrence. A complete disappearance of a lipoma does not take place in the case of extreme general emaciation of the individual.

Lipomata are sometimes observed even in new-born children—for

example, as tumors developing in or over the cleft-formations of spina bifida—but they occur much more frequently in later years. The most common seats of these growths are the subcutaneous tissues of the back,

FIG. [illegible].—Lipomyxoma of the back (Müller's fluid, Van Gieson's). a, Large fat-cells; b, c, fat-cells in which the fat is broken up into little droplets; d, mucous tissue; e, blood-vessel. × 200.

buttocks, neck, axilla, abdomen, and thigh; but they are found also in the intermuscular connective tissue, subserous fat tissue, in the kidneys, intestine, mammary gland, under the aponeurosis of the forehead, in the meninges, skin, fingers, lymph-glands, joints, etc. They may occur as multiple growths, and in such cases may be symmetrically distributed. In man there may occur a formation of fat tissue about the neck and throat, leading to nodular and lobulated disfigurations of the skin of this region, and giving occasion for the designation *fatty collar* (Madelung). The development of fat in these cases takes place partly in the subcutaneous tissue, partly in and under the fascia and between the muscles. An abnormal development of fat in an extremity may give rise to a condition of *lipomatous elephantiasis*. Should the process extend to the trunk and upper extremities, etc., conditions are established which resemble very closely general obesity.

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(*d*) *Chondroma.*

§ 105. A **chondroma** or **enchondroma** is a tumor consisting essentially of *cartilage.* The amount of connective tissue taking part in the structure of the tumor, in part covering its surface or accompanying the blood-vessels into

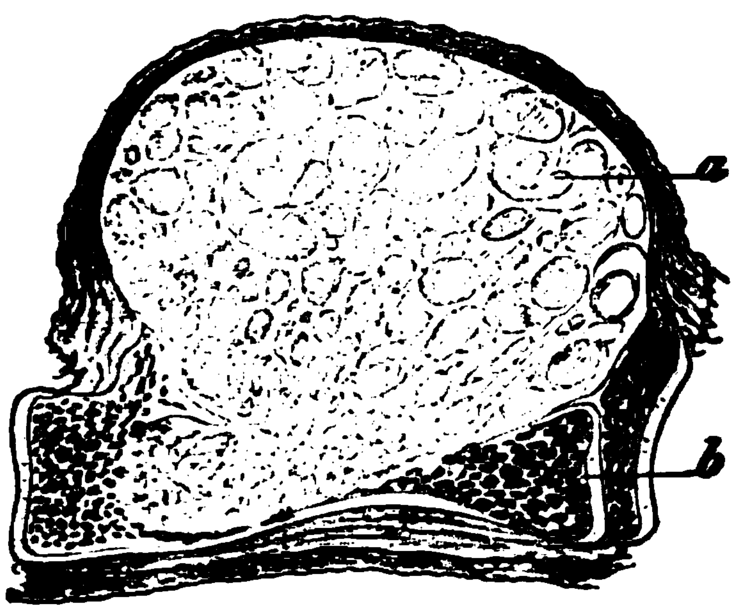

FIG. 255.

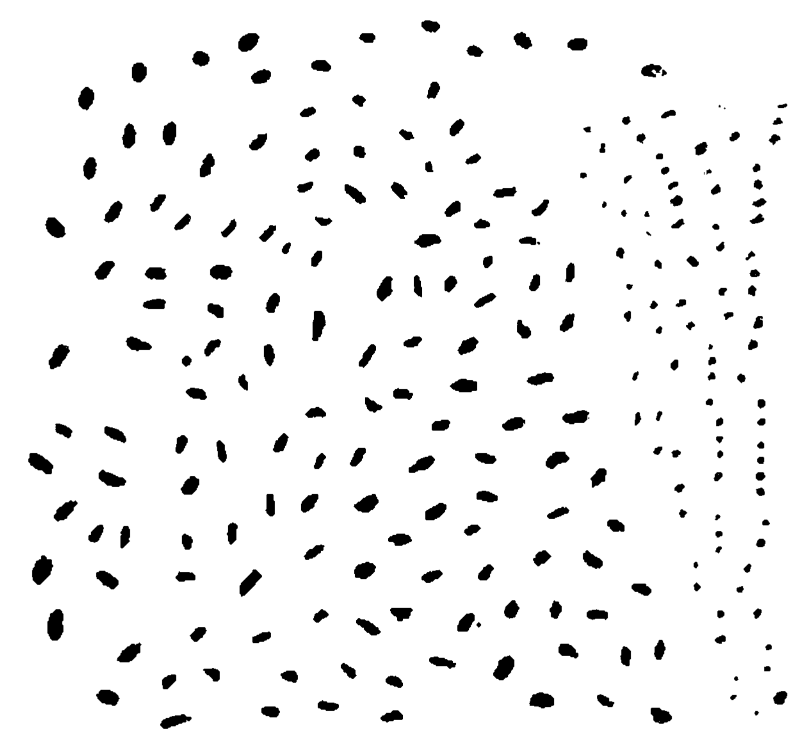

FIG. 256.

FIG. 255.—Periosteal chondroma of a digital phalanx, seen in longitudinal section. *a*. Chondroma; *b*, phalanx. Natural size.

FIG. 256.—Section from a chondroma of the ribs (hæmatoxylin, carmine). *a*, Cartilage rich in small cells; *b*, cartilage rich in large cells. × 80.

its interior, is so slight as to fall completely into the background when compared with the cartilage.

Chondromata develop chiefly in those places where cartilage is found normally—that is, in the osseous system or in the cartilages of the respiratory tract; but they also occur in tissues which normally possess no cartilage—for example, in the salivary glands, particularly in the parotid, and in the testicles, and more rarely in other organs. In the bones they develop from remains of cartilage which persist after ossification, in the case of bones developing from cartilage; but more often take their origin from the periosteum and endosteum (Fig. 255). They form tumors which vary greatly in size. The small ones are usually spherical (Fig. 255); the larger ones nodular or lobulated. The individual nodules are often separated from one another by connective tissue. Not infrequently they are multiple, particularly in the skeleton, and here again of most frequent occurrence in the hands and feet and also in the testicles.

The tissue of an enchondroma presents most often the characteristics of hyaline cartilage (Fig. 256), more rarely that of reticular or fibrous cartilage. At the periphery of the tumor the cartilage passes over into connective tissue, which forms a kind of perichondrium.

The number, size, form, and grouping of the cartilage cells vary greatly in different cases and also in different parts of the same tumor. Many enchondromata are very cellular (Fig. 256), others poor in cells, many contain large cells, others small cells, or both large and small cells.

The cells are sometimes surrounded by the so-called capsule, at other times not; sometimes they lie in groups inside of the mother-capsule, at other times they are more regularly distributed. All the varieties of cartilage occurring normally in the organism are found in enchondromata. Accordingly the cells vary in form, the majority showing the familiar spherical form, but spindle and stellate cells are not rare, particularly in the neighborhood of the connective-tissue bands which divide the tumor into nodules or surround it as a whole. Cartilage, the perichondrium, endosteum, periosteum, and different forms of connective tissue may form the matrix of enchondromata. Those arising from cartilage or bone are known as *ecchondroses*.

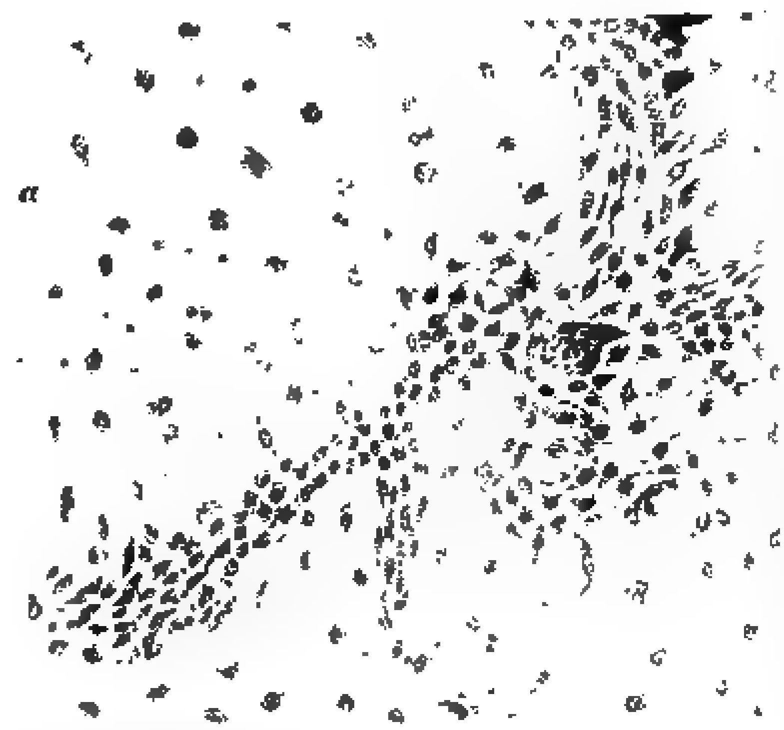

FIG. 257. Chondromyxosarcoma parotidis (alcohol, carmine). *a*, Cartilage; *b*, sarcomatous tissue; *c*, myxomatous tissue; *d*, cartilage in process of liquefaction and being converted into sarcomatous and myxomatous tissue. × 80.

The tissue of enchondromata very frequently suffers retrogressive metamorphoses. The ground-substance in large tumors shows a tendency to undergo in areas a mucoid degeneration and liquefaction. This may lead

FIG. 258.—Periosteal chondroma of the calcaneus, with areas of calcification (Müller's fluid, hæmatoxylin). *a*, Hyaline cartilage; *b*, *c*, calcified cartilage. × 225.

either to the formation of *mucous tissue* (Fig. 257, *c*), thus giving rise to a *chondromyxoma;* or to a total liquefaction of the ground-substance with destruction of the cells, thus forming *degeneration-cysts* containing fluid.

FIG. 259.—Osteochondroma of the humerus (alcohol, picric acid, hæmatoxylin, carmine). *a*, Hyaline cartilage; *b*, bone; *c*, cartilage which is becoming converted into bone; *d*, blood-vessel. × 250.

In other cases the cartilage may become calcified (Fig. 258, *b*, *c*), or true *bone* may be formed (Fig 259, *c*, *b*), so that the tumor must be termed an **osteochondroma.** Through a marked proliferation of the cartilage cells *sarcomatous tissue* may be developed, the tumor becoming changed to a **chondrosarcoma** (Fig. 257, *b*).

The enchondromata are, on the whole, benign tumors, although metastases may occur following a rupture into a lymph- or blood-vessel.

In the region of the spheno-occipital suture, in the median line of the clivus, there is not infrequently found a small tumor which has been designated **ecchondrosis physalifera sphenooccipitalis** (*Virchow*). It either lies beneath the dura, or at its highest point breaks through this membrane and penetrates into the arachnoid and pia. In its typical form the tumor consists of bladder-like cells, resembling plant-cells; and takes its origin partly from the bone-marrow, partly from the surface of the bone. Cartilage and bone tissue may be associated with the peculiar tumor tissue, and for this reason *Virchow* regarded the growth as a chondroma arising from remains of the spheno-occipital cartilage and characterized by a peculiar vacuolar degeneration of the cells. The peculiar character of the tissue, however, favors the view advanced by *H. Müller*, and recently supported by *Ribbert*, that the growth is a product of a proliferative activity of remains of the chorda (*chordoma*). It is probable that it is only a peculiar chondroma developing from the endosteum or periosteum.

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(*e*) *Osteoma.*

§ **106**. The term **osteoma** is applied to tumors which consist of *osseous tissue*. Such growths arise chiefly from the bones of the skeleton (Figs. 260–262), but may develop elsewhere.

The new-growths of bone arising in connection with the skeleton have been variously designated according to their location and relations. A small circumscribed new-growth of bone attached to old bone is called an *osteophyte;* when of a larger size and more tumor-like, an *exostosis.* Circumscribed formations of bone inside of bones are known as *enostoses.* New-growths of bone not attached to old bone are classed as follows: *movable periosteal exostoses*, which have their seat in the periosteum but are separated from the bone; *parosteal osteomata*, lying near the bone; *disconnected osteomata*, which are situated some distance from the bone, in the muscles and tendons; and, finally, *heteroplastic osteomata*, which occur in other organs, as, for example, in the lungs, mucous membrane of the trachea, in the skin, arteries, mamma, etc.

Excrescences on the teeth, consisting of cement-substance, are known as *dental osteomata;* those consisting of dentine, as *odontomata.*

FIG. 260.—Ivory-like exostosis of the parietal bone. Natural size.

According to their structure, osteomata may be divided into hard or *eburneous osteomata* (*osteoma durum* or *eburneum*) (Figs. 260 and 262), and softer *spongy* forms (*osteoma spongiosum* or *medullare*) (Figs. 261 and

263). The former consist of firm, compact tissue like that of the cortical portion of the long bones, and possess very narrow nutrient canals (Fig. 262, *a*); the latter are made up of narrow, delicate bony trabeculæ and wide medullary spaces (Fig. 263), and resemble spongy bone in structure.

The surface is sometimes regular and smooth, so that the whole tumor presents the form of a cone (Fig. 260), or of a sphere, or a pedunculated button; or it may be irregular, rough, and nodular, without definite resemblance to any given form (Fig. 261). The first variety occurs particularly in the eburneous forms, which are found most frequently as exostoses upon the skull (Figs. 260 and 262); the latter in the spongy exostoses and the disconnected and heteroplastic osteomata, such as are found, for example, in the falx of the dura mater (Fig. 263).

Osteomata may occur as *single* or *multiple* tumors, the latter mode of occurrence being relatively common. The ivory-like exostoses of the cranium and the osteomata of the dura mater are very frequently of currence, and circumscribed bony :en appear in great numbers on ɪf the extremities and trunk. In the epiphyseal ends of the bones ›ints of insertion of tendons, or same time, are the favorite seats ment. It is probable that such e to be referred to an inherited on of the part affected to over-ɔ disturbances in the development eton. At times a hereditary fac- demonstrated. The bony plates s, which in rare cases develop in the lung or in the mucous membrane of the air-passages, may also occur in large numbers.

FIG. 261. Exostosis cartilaginea of the upper diaphysis of the tibia. Reduced about one-half.

The development of the bone takes place partly through the formation of osteoblasts, as described in § 83, and partly through metaplasia of formed tissues (§ 88). The matrix is formed chiefly from the connective tissue of the periosteum, as well as that of the tissue from which the osteoma arises; and also from that of the perichondrium and endosteum. If an exostosis develops in such a manner that cartilage is first formed from the proliferating periosteum or bone-marrow, and from this cartilage bone is later developed, it is called a *cartilaginous exostosis* (Fig. 261); when the exostosis is formed directly from the proliferating periosteum without an intermediate stage of cartilage, it is known as a *connective-tissue exostosis* (Figs. 260, 262, and 263).

The combination of connective tissue and bone in a tumor, in such a manner that the connective tissue represents a chief constituent of the growth and does not simply represent the periosteum and bone-marrow

of the bone, gives rise to an **osteofibroma**. This is a very common tumor of the osseous system. The abundant production of bone in a

FIG. 262.—Ivory-like osteoma of the parietal bone, seen in frontal section. *a*, Osteoma; *b*, skull-cap. Eight-ninths natural size.

chondroma leads to the formation of an **osteochondroma** (Figs. 259 and 264); these tumors are likewise usually found in the long bones. The

FIG. 263.—Osteoma of the dura mater (alcohol, picric acid, hæmatoxylin, carmine). × 40.

new-growth may develop in the periosteum (Fig. 264, *c*) or in the endosteum (*a*, *b*). An abundant formation of bony trabeculæ (*f*, *h*, *k*) in the cartilage (*e*, *g*, *i*) gives to the tissue a firm, hard consistence.

Many of the new-growths of bone which come under observation are not tumors in the strict sense of the term, but are malformations of the skeleton or hyperplasias resulting from excessive growth or from inflammatory processes. This is true particularly of many osteophytes and exostoses, and also in part of the parostoses and the disconnected osteomata (bone formations in lymph-glands and lungs). The bony plates not infrequently found in the falx of the dura, and which have a normal bone-marrow (Fig. 263), are to be regarded as misplaced portions of the skeleton. The formations of bone known as *rider's bone* and *drill-bone*, which are found in the adductors of the thigh and in the deltoid muscle, as the result of riding and the repeated shouldering of arms, are to be regarded as tumors, which develop from a *congenital anlage*, in that the connective tissue of the muscle shows characteristics which ordinarily belong only to the periosteum and bone-marrow. The so-called *myositis ossificans*—a peculiar disease of the muscles, characterized by a progressive ossification of their connective tissue during childhood—is to be similarly interpreted.

Fig. 264.—Osteochondroma of the humerus (alcohol, picric acid, hæmatoxylin, carmine). *a*, Cortical portion of the humerus; *b*, medullary cavity; *c*, periosteal deposit of bone; *d*, normal Haversian canals; *e*, dilated Haversian canals filled with cartilage, containing newly formed bone at *f*; *g*, cartilage with bone-trabeculæ *h*, formed by the periosteum; *i*, cartilage with newly formed bone-trabeculæ, arising from the endosteum; *k*, *l*, old bone trabeculæ; *m*, remains of marrow-tissue. Pocket-lens magnification.

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(*f*) *Hæmangioma and Lymphangioma.*

§ 107. Under the term **angioma** are grouped those *tumor-like formations in the structure of which blood-vessels* or *lymph-vessels constitute such an important part as to determine the character of the tumor.*

Vascular tumors arising from blood-vessels are called **hæmangiomata**, or *angiomata* in the restricted sense of the term; those arising from lymph-vessels are designated **lymphangiomata.** Such tumors for the greater part represent formations which may be regarded as *malformations* of a more or less extensive vascular area. Of the hæmangiomata there may be distinguished four chief varieties: *hæmangioma simplex, hæmangioma cavernosum, hæmangioma hypertrophicum,* and *angioma arteriale racemosum.*

A **hæmangioma simplex** or **teleangiectasia** is a tissue-formation in which, within a ground tissue of normal occurrence in the body, there is

FIG. 265.—Teleangiectasis of the panniculus adiposus of the abdominal wall (formalin, hæmatoxylin, eosin). *a*, Blood-vessels filled with blood; *b*, adipose tissue. × 60.

found an *abnormal increase in the number or in the size of the capillaries and veins, whose structure in part is essentially changed.*

Such formations occur most frequently in the skin and subcutaneous tissue. They are usually congenital, but increase in size after birth. They are designated **vascular nævi**, and are often found in places

where fetal clefts have closed (*fissural angiomata*). Of a tumor in the ordinary sense it is often scarcely possible to speak, since the skin may show no tumor-like elevation. On the other hand, there occur extensive

FIG. 266.—Dilated capillaries of a teleangiectatic tumor of the brain, isolated from a portion of tumor by means of shaking. × 200.

teleangiectases of the skin and subcutaneous tissue, presenting either as circumscribed growths or as flat, occasionally nodular thickenings of the skin, which may with propriety be termed tumors. The smooth *nævus vasculosus*, on the other hand, appears as an extensive superficial substitution of the skin by another tissue. The color of the affected portion of the skin is either *bright red* (*nævus flammeus*) or *bluish-red* (*nævus vinosus*). The line of demarcation between the normal and affected skin is usually not a sharp one; around the edge and in the neighborhood of the chief area of discoloration there are often found little, circumscribed red spots appearing as outrunners of the process.

FIG. 267.—Angioma cavernosum cutaneum congenitum (Müller's fluid, hæmatoxylin). *a*, Epidermis; *b*, corium; *c*, cavernous blood-spaces. × 20.

The red color is due to the dilated blood-vessels which are situated either in the corium or in the subcutaneous fat tissue (Fig. 265, *a*); and cases occur in which large areas of the subcutaneous adipose tissue present a red appearance as a result of the pathological development of blood-vessels.

More rarely than in the skin and subcutaneous tissues, there occur similar angiomata in other places: in glands (mamma), bones, brain (Fig. 266), and spinal cord and their membranes. Not infrequently, on the other hand, there are found analogous vascular changes in tumors, as. for example, in gliomata or sarcomata.

If the vessels, which are usually abnormally abundant, are isolated, it becomes evident that the capillaries, or also the small veins (*angioma simplex venosum*), are more or less dilated. These dilatations (Fig. 266) are either spindle-shaped or cylindrical, but may be saccular or spherical, and the different forms of dilatation may be combined in the greatest variety of ways. The dilated blood-vessels are united with

FIG. 266.—Angioma cavernosum hepatis (Müller's fluid, hæmatoxylin, eosin). *a*, Liver tissue; *b*, angioma. × 100.

each other by capillaries of normal size or of moderately increased calibre. The walls of the vessels are thin—that is, in comparison with normal capillaries they are but slightly thickened.

A **hæmangioma cavernosum** or *tumor cavernosus* is a *vascular tumor consisting essentially of a cavernous spongy tissue*, whose structure suggests that of the corpus cavernosum or spongiosum of the penis (Figs. 267 and 268). Through the filling of the spaces with blood these tumors present a bluish-red or dark red color.

The cavernous angioma, like the angioma simplex, occurs chiefly in the skin (Fig. 267, *c*) and subcutaneous tissues, where during the period of development it appears as a pathological formation of the vascular system. At times it forms only a small bluish-red spot (*nævus vasculosus vinosus*); at other times, a smooth, elevated (Fig. 267), or slightly nodular bluish-red wart (*nævus vasculosus prominens, verruca vasculosa*); or, finally, a circumscribed bluish-red discoloration or thickening of the skin. In the event of an extensive development of cavernous tissue in the subcutaneous or intermuscular connective tissue, there may result

large tumors and elephantiasis-like disfigurations of portions of the body (elephantiasis hæmangiomatosa).

Within the body the cavernous angioma is found most commonly in the liver (Fig. 268, *a*, *b*), but may develop also in other organs:

FIG. 269.—Angioma simplex hypertrophicum (formalin, hæmatoxylin). *a*, Vessels containing blood; *b*, empty and collapsed thick-walled blood-vessels rich in nuclei. × 100.

kidney, spleen, intestine, bladder, bones, muscles, uterus, brain, etc. In the liver it appears in the form of dark-red areas, varying in size from that of a pin-head to several centimetres in diameter. They take the place of the liver tissue, and are not elevated, or but slightly, above the liver surface.

The width of the blood spaces and the thickness of the trabeculæ vary greatly in different cases; the angioma may in portions or throughout be composed of fibrous tissue, in that more fibrous tissue was formed in the beginning, or fibrous proliferations have taken place later as sequelæ to the thrombosis. The blood spaces are lined with endothelium; at times smooth muscle-fibres may be demonstrated in their walls, and the interstitial tissue is often rich in elastic fibres (Brüchanow). The tumor is usually sharply outlined from the neighboring structures by connective tissue. Usually no liver cells are found in the trabeculæ, but varieties do occur in which the latter in part enclose such, and in which, further, the blood spaces here and there pass over into the liver-capillaries, such a communication ordinarily not taking place.

FIG. 270.—Angioma simplex hypertrophicum cutaneum et subcutaneum (alcohol, carmine). In the middle of the section is the duct of a sweat-gland cut transversely. × 200.

The cavernous angioma of the liver occurs in old individuals, and also in infants and children of different ages, and not infrequently is of mul-

tiple occurrence. It is probably caused by a local disturbance of development, which proceeds from the vessels of Glisson's capsule or from the intra-acinous capillaries; and is characterized by an abnormal development of the blood-vessels at the expense of the other tissues. The growth is slow and limited; ordinarily the liver-cells in the immediate neighborhood show no signs of degeneration. During the period of rapid growth (Brüchanow), there may occasionally be demonstrated in children the presence at the periphery of the growth of a cellular granulation tissue, in which the blood-vessels consist of delicate endothelial tubes having a narrow lumen.

The **hæmangioma hypertrophicum**, in its most typical form (*hæmangioma simplex hypertrophicum*), occurs most frequently in the skin and subcutaneous tissues, where it forms circumscribed nodules similar in part to the soft, smooth warts. The pathologically altered vessels may lie in the papillæ and corium as well as in the subcutaneous tissue, and either form narrow tubes filled with blood (Figs. 269, *a*, and 270), the

FIG. 271.—Angioma cavernosum hypertrophicum (angioendothelioma) of the skull-cap (Müller's fluid, hæmatoxylin). *a*, Blood-vessel with flattened endothelium; *b*, blood-vessel with cubical and cylindrical endothelium. × 250.

walls of which are more or less thickened and abnormally cellular, or else solid cords of cells (Fig. 269, *b*), which are either collapsed, thick-walled vessels, or possess no lumen whatever.

In very rare cases it happens that in angiomata, which from the calibre of the vessels bear the character of cavernous angiomata, there occurs a hypertrophy of the vessel-walls; and this hypertrophy is due to the fact that the flat endothelial cells become changed into cubical and cylindrical cells (Fig. 271, *b*). Such a tumor may be classed as an *angioma cavernosum hypertrophicum*, or as a *blood-vessel-endothelioma*, or *hæmangioitic endothelioma;* the last term being in particular applicable when, as a result of the marked proliferation and multiplication of the endothelium, there are produced nests of large cells which fill up the blood-vessels (compare Endothelioma, §§ 114 and 115).

A **cirsoid aneurism**, or **angioma arteriale racemosum**, or **angioma arteriale plexiforme** (Fig. 272), is a condition in which the arteries of an entire vascular area are *dilated, tortuous,* and *thickened,* so that there is

formed a convolution of enlarged and thickened arteries. To the palpating finger they feel like a bunch of earth-worms. Many of these angiomata, which occur particularly upon the head, and which may cause

Fig. 272.—Angioma arteriale plexiforme arteriæ angularis et frontalis dext. et sin.

erosion of the cranial bones, arise from congenital anlage; others appear to be acquired, and develop after a traumatism, but it is possible that special conditions may have existed before the trauma.

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See also § 116.

§ 108. **Angioma lymphaticum** or **lymphangioma** is a tumor composed of a tissue the greater part of which is made up of *dilated lymph-vessels*. The following different forms may be distinguished: *lymphangioma simplex* or *teleangiectasia lymphatica* (Fig. 273); *lymphangioma cavernosum* (Fig. 274); *lymphangioma cystoides*; and *lymphangioma hypertrophicum*. The cavities of these tumors usually contain a clear, light-colored lymph, but more rarely it is milky and contains lymphocytes, mononuclear and polynuclear leucocytes, and usually also eosinophile cells. The walls consist of connective-tissue trabeculæ of varying thickness and containing more or less involuntary muscle; the spaces are lined with endothelium.

In the **lymphangioma simplex** (Fig. 273) the lymph-vessels of a more or less extensive area are dilated and their walls for the greater part are thickened. In the **cavernous lymphangiomata** the number of

FIG. 273.—Weeping subepithelial lymphangioma of the skin (alcohol, carmine). *a*, Corium; *b*, epithelium *c*, *d*, lymph-spaces. × 14.

lymph-vessels is still greater, their spaces are larger, and the intervening tissue is less abundant, so that, even to the naked eye, the tissue presents a spongy appearance. The **cystoid lymphangiomata** contain cysts varying in size from that of a pea to a walnut. The tissue between the dilated lymph-vessels consists, according to the location of the tumor, either of connective tissue (Fig. 273), fat tissue (Fig. 274, *c*), muscle, or some other tissue. At times nodes of lymphadenoid tissue may be enclosed (*c*), and may present evidences of active proliferation.

Lymphangiomata are sometimes congenital; at other times they make their first appearance at a later period of life.

The congenital forms occur particularly as different varieties of ectasia of lymph-vessels, and are found chiefly in the tongue (*macroglossia*), palatal arch, lips (*macrocheilia*), skin (*nævus lymphaticus*), subcutaneous tissue, in the neck (*hygroma colli congenitum*), vulva, etc. The *lymphangiomata of the skin* spread over more or less extensive areas of the skin, and form either smooth or irregular elevations of the same. If the blood-vessels are numerous the growth may have a red color. The rupture of dilated lymph-vessels lying immediately beneath the epithelium (Fig. 273, *d*) may give rise to a moist condition of the surface and

FIG. 274.—Lymphangioma cavernosum subcutaneum (alcohol, alum-carmine). *a*, Ectatic lymph-vessels; *b*, connective tissue; *c*, adipose tissue; *d*, large blood-vessels; *e*, cellular areas. × 200.

eventually to a lymphorrhœa. The extension of the cavernous development of the lymph-vessels over large areas of the skin and subcutaneous tissue may give rise to *elephantiasis-like disfigurations* of the part affected. Not infrequently the intervening connective tissue also takes part in the hypertrophic growth, or there develops a fibrous elephantiasis in connection with lymphangiectasia.

In rare cases chyle-containing growths (*chylangiomata*) are found in the intestinal wall or mesentery. *Cystic lymphangiomata* are also found rarely in the *peritoneum* as pedicled cysts.

The pathological formations which may be classed as **hypertrophic lymphangiomata** represent peculiar changes of the skin, which are either congenital or develop in early youth. They are commonly known as pigmented moles, lentigines, freckles, and fleshy warts.

The *pigmented moles*, or *nævi pigmentosi*, or *melanomata*, form larger or smaller smooth areas which are not elevated above the general surface of the skin (*nævus spilus*), or prominent warty growths (*nævus prominens, nævus verrucosus*). When covered with hair, as is frequently the case, they are called *hairy moles* (*nævus pilosus*). In color they are usually light brown or dark brown, or even black (Fig. 275); and are usually

covered by epidermis of normal thickness, more rarely by hypertrophic epithelium. They are usually small, but may be as large as the palm of the hand, or under certain conditions may cover a large part of the body surface.

Lentigines appear at any time after birth, and upon any part of the body surface; and when once formed they remain for life. They form sharply circumscribed yellow to brownish-black spots closely resembling the little pigmented nævi; and vary in size from that of a pinhead to that of a lentil.

Freckles or *ephelides* are small, irregularly outlined, serrated, pale-brown spots, which are not elevated above the surface of the skin. They occur in young individuals, particularly on the face, hands, and arms, rarely on other portions of the body; and may either remain permanently or disappear after a longer or shorter time. The pigmentation is favored by exposure to sunlight.

Fleshy moles (*verrucæ carneæ*) are non-pigmented, circumscribed, smooth (Fig. 276) or slightly irregular, or more rough and papillary (Fig. 278) prominences of the skin, over which the epidermis is at times normal, at other times somewhat hypertrophic (Fig. 278, *a*).

Fig. 275. — Large hairy and pigmented nævus of back, buttocks, and thighs, with scattered smaller pigmented spots over the remaining portions of the body. (After Röhring.) (Reduced from original.)

In all of the pathological formations just described the connective-tissue framework encloses *collections of cells*, either in round or cord-like masses (Figs. 276, 277, 278, *d*, d_1), which lie partly in the papillæ and partly in the corium; and are the more abundant the more the growth pro-

Fig. 276.—Lymphangioma hypertrophicum. Section through a small, soft, smooth wart (formalin, hæmatoxylin, eosin). × 40.

FIG. 277.—Lymphangioma hypertrophicum. Rounded summit of a large, soft, smooth wart (formalin, hæmatoxylin, eosin). Sharply outlined cell-nest in corium. × 250.

jects above the surface of the skin. In the pigmented forms the cells of the cell-nests may also contain the pigment (chiefly in the form of brown or yellow granules, but in part diffused throughout the substance

FIG. 278.—Section through two papillæ of a papillary fleshy wart (alcohol, carmine). *a*, Thickened horny layer of the epidermis; *b*, epithelial pearls; *c*, rete Malpighii; *d*, nests and strands of cells in the papillæ; d_1, nests and strands of cells in the reticular layer; *e*, connective tissue. × 50.

of the cells); though often the pigment lies chiefly within the connective tissue cells of the fibrous portions of the growth.

The cells of the cell-nests are relatively large (Fig. 277), possess an abundant protoplasm, and a bright, bladder-like nucleus. Their position and appearance justify the assumption that they represent *the products of the proliferation of the endothelial cells of the lymph-vessels.* In rarer cases similar formations arise from the blood-vessels (hæmangioma hypertrophicum). Accordingly, it would seem proper to class these growths with the endotheliomata or lymphangiosarcomata, but their limited growth makes their classification as lymphangiomata more appropriate (see § 114). The cell-nests of the hypertrophic lymphangioma may in part spread out more diffusely through the tissues (as is the case with the hypertrophic hæmangioma), so that the peculiar structure of the growth may be lost. In rare cases there may develop a combination of hypertrophic lymphangioma and lipoma.

Unna, *Kromayer*, *Delbanco*, and *Marchand* hold the view that the cell-nests of the cellular nævi are of epithelial origin, and represent misplaced portions of the surface epithelium; and *Kromayer* goes so far as to assume a metaplasia of epithelium into connective tissue. Preparations showing the first stages of the development of nævi are not accessible to me; but a thorough study of nævi and fleshy warts of a later stage does not show any connection between the cell-nests and the epithelium; and consequently I hold the opinion—notwithstanding the investigations of the above-named authors—that the view given above in the text, in regard to these nævi and fleshy warts, harmonizes most perfectly with their anatomical nature and clinical behavior, both in their fully developed condition as well as when they undergo a transformation into malignant sarcomata. That in individual cases the cell-nests lie close to the epithelium is no proof of a genetic relationship, since the ordinary lymphangiomata also lie close to the epithelium (Fig. 273, *d*).

According to investigations by *Jadassohn* and *Lanz* the cellular warts can be transplanted from one individual to another by an intra-epidermoidal inoculation of cell-masses.

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(*g*) *Myoma.*

§ 109. A **myoma** is a tumor consisting essentially of *newly formed muscle-fibres.* According to the nature of the muscular elements, myomata are divided into *leiomyomata* formed of *unstriped muscle,* and *rhabdomyomata* composed of *striped muscle.*

The **leiomyoma,** or *myoma lævicellulare,* occurs most frequently in the uterus, more rarely in the tubes, uterine ligaments, labia majora, mus-

FIG. 279.—Myoma of the uterus (Müller's fluid, hæmatoxylin, eosin). × 300.

cularis of the gastro-intestinal tract and urinary passages; and may form spherical, nodular tumors of varying size. In rare cases it is found also in the skin and subcutaneous tissues, forming in this location small

nodules occasionally reaching the size of a pigeon's egg. Leiomyomata occur as either single or multiple tumors; and may appear during childhood, or even develop under certain conditions during intrauterine life (Marc).

In muscular organs the new-growth proceeds from the muscularis, and forms during its development bundles of muscle-fibres (Fig. 279) which are interwoven in different directions, and consequently present

FIG. 280.—Angiomyoma subcutaneum dorsi (alcohol, hæmatoxylin, eosin). *a*, Cavernous blood-vessels; *b*, strands of muscle cut longitudinally; *c*, same cut transversely; *d*, connective tissue; *e*, artery with hypertrophic muscularis; *f*, groups of lymphoid cells. × 46.

in sections a variety of pictures according to the directions in which the bundles are cut. Myomata of the uterus may contain included uterine glands. Those developing in the dorsal wall of the body of the uterus and near the angles of the tubes, or in the inguinal region, may contain a varying number of gland-tubules which arise from the Wolffian body (von Recklinghausen); such tumors may be designated *adenomyomata*. They are distinguished from the ordinary spherical myomata which are sharply circumscribed, by the fact that their boundaries are not sharply defined. Eventually some of the glands may become cystic as the result of the accumulation of secretions. According to Ricker, Pfannenstiel, and others, the ordinary uterine myomata as well as those of the vaginal vault may also contain epithelial tubes, which probably owe their origin to inclusions of portions of the duct of Müller. In the skin and subcutaneous tissue the new-formation of muscle-fibres proceeds in the first place from the muscularis of the vessels (Fig. 280), which thereby become thickened (*a*), and at the same time give rise to free strands of muscle-fibres (*b*). A pathological new-formation of blood-vessels may be associated with that of muscle (*a*), so that tumors arise which are designated *angiomyomata* (Fig. 280). According to observations by Jadassohn

and others, multiple myomata of the skin may take their origin either from the arrectores pilorum or from the muscle-cells of the sweat-glands.

A certain amount of connective tissue always takes part in the formation of a large myoma, and often assumes such importance that the tumor may with propriety be called a **fibromyoma** or **myofibroma.** For example, the majority of the uterine myomata are fibromyomata. The fibrous connective-tissue portions of the tumor appear glistening white, the muscular portions more reddish-white or clear reddish-gray. The spindle-shaped muscle-fibres may be isolated by teasing a bit of the tumor or by maceration of the same for twenty-four hours in a twenty-per-cent nitric-acid solution or for twenty to thirty minutes in a thirty-four-per-cent solution of potassium hydroxide. In longitudinal sections the muscle-fibres are most easily recognized by their rod-shaped nuclei (Figs. 279, 280), as well as by the regular structure of the cells in bands or strands. In cross-section the muscle-cells appear as small flattened cells containing in their centres the transversely cut nuclei (Fig. 279).

The leiomyomata are benign tumors, but often reach a very large size, and sometimes undergo a sarcomatous proliferation and set up metastases. The muscle-cells themselves may change their character and proliferate or the intermuscular connective tissue may take on a sarcomatous proliferation. In fibromyomata of the uterus there not infrequently occur fatty degeneration and softening, which may lead to the disintegration of the tumor or to the formation of cystic cavities. Calcification and bone-formation may also occur. Through degeneration and atrophy of the muscle-fibres a myofibroma may become transformed into a fibroma.

A **rhabdomyoma** (Zenker), or *myoma striocellulare* (Virchow), is on

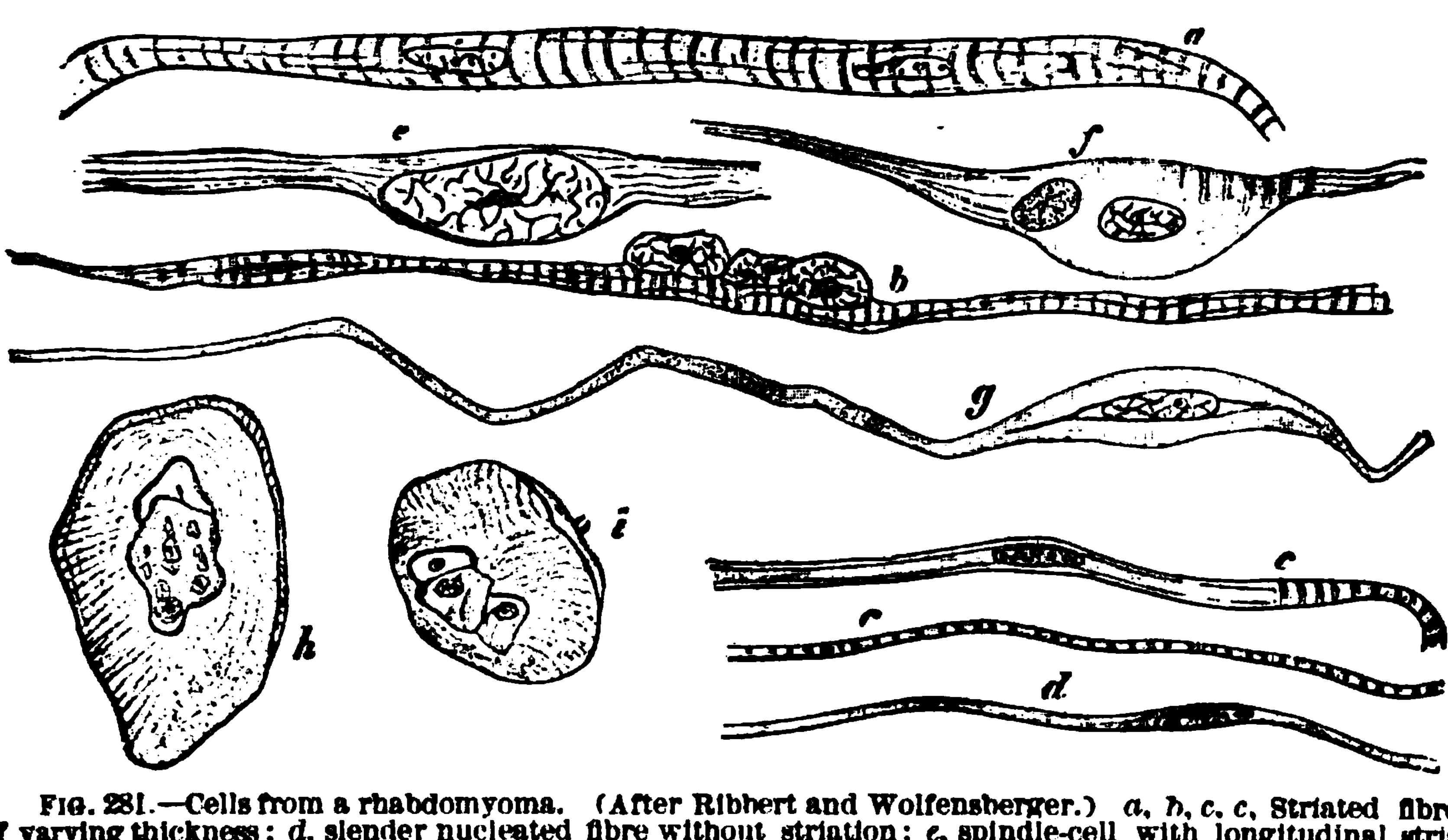

FIG. 281.—Cells from a rhabdomyoma. (After Ribbert and Wolfensberger.) *a*, *b*, *c*, *c*, Striated fibres of varying thickness; *d*, slender nucleated fibre without striation; *e*, spindle-cell with longitudinal striation; *f*, spindle-cells with longitudinal and transverse striation; *g*, spindle-cells, without striation, with elongated processes; *h*, *i*, round cells with concentric and radial striation.

the whole a rare tumor. Its most characteristic feature is the presence of striated muscle-fibres, which in part are fully developed and in part undeveloped. When well developed the muscle-fibres form multinuclear bands of varying width, which present a cross-striation (Fig. 281, *a*, *b*, *c*), and in part also a longitudinal striation (*e*, *f*). The undeveloped forms consist of narrow bands without transverse striations (*d*); of spindle-cells with long-drawn-out thread-like processes without transverse

striation (*g*) or with partial striation (*f*); or, further, of round cells of different sizes, which present either a radial or a concentric fibrillation or striation (*h, i*). Besides these there are also cells which possess no especial characteristics, so that it is impossible to decide whether they are young undeveloped muscle-cells or connective-tissue cells. The bands as well as the spindles are usually arranged in interlacing bundles. It is usually not possible to demonstrate with certainty the presence of a sarcolemma on the surface of the fibres; but various delicate membranes have been described by different authors, which probably are to be regarded as representing portions of a sarcolemma.

Rhabdomyomata of the heart, in so far as they do not consist of a formation of delicate transversely striated muscle-fibres, are made up of a delicate network supported by connective-tissue bands, in the clear spaces of which network there lie spider-like cells, whose processes are partly free, and partly continuous with the reticulum. According to Seiffert, these cells are to be regarded as enlarged embryonal muscle-cells, which, in the event of an overproduction of the structureless protoplasmic portion, have formed no transversely striated covering.

Rhabdomyomata occur in the kidney or its pelvis, in the testicles, uterus, the vagina, bladder, muscles, heart, nerves, subcutaneous tissue, mediastinum, œsophagus, etc., and form nodular, or, in case they are situated on the surface of a mucous membrane, papillomatous and polypoid tumors, which vary greatly in size. They develop from striped muscle, possibly also from smooth muscle (uterus). In the kidneys and testicles they either form circumscribed nodules, or lead to a total destruction of the organ. The origin of the tumor in these cases is probably from misplaced anlage of muscle-tissue; and accordingly such growths are most frequently congenital. They may, however, develop first at an advanced age. Occasionally they enclose other tissues, for example, cartilage. Moreover, muscle-fibres of corresponding stages of development occur in the *complex tumors* of the testicles and kidneys (see Teratoma).

If a tumor contains only a few cells which can be definitely recognized as muscle-fibres, while the majority of the cells have no specific character, the tumor is ordinarily designated a *rhabdomyosarcoma*.

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(*h*) *Glioma and Neuroglioma Ganglionare.*

§ 110. A **glioma** is a tumor which develops from the *cells of the supporting tissue of the central nervous system* (neuroglia), and in its fully developed condition consists essentially of these cells. In the brain the gliomata form tumors, which for the most part are not sharply defined from the normal brain-substance, but pass into the latter by insensible gradations. At times they appear simply as local swellings of the brain, and only the difference in color and the disappearance of the normal tissue-contrasts between the different elements of the brain, give evidence to the eye that a tumor is present. In the spinal cord they arise most frequently in the neighborhood of the central canal, and may extend over a large portion of the cord.

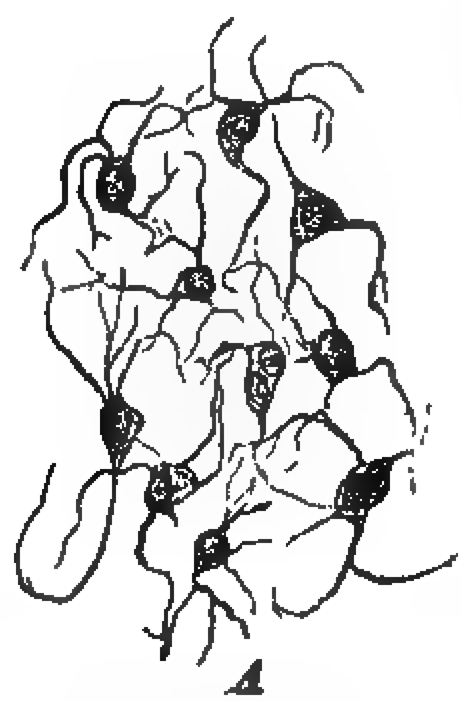

Fig. 2?2.—Glioma cerebri. *A*, Cells isolated by teasing and stained with carmine. *B*, Section from same glioma after hardening in Müller's fluid (Bismarck brown). × 350.

Their appearance varies greatly; sometimes they are light-gray, somewhat translucent, and similar in color to that of the cortex, and moderately firm in consistence; at other times they are more grayish-white, denser, and firmer; and again they are not infrequently grayish-

red or dark red in color and are then sharply circumscribed from the surrounding brain substance. In the last case they are traversed by numerous large vessels. Gliomata well supplied with blood often contain hæmorrhagic areas. Fatty degeneration, softening, and destruction of the tissue are also of common occurrence.

A section of a fully developed glioma shows under the microscope a network of extremely delicate glistening fibrillæ (Fig. 282, *B*), in which are imbedded numerous short oval nuclei. About the nuclei there is but a scanty amount of protoplasm, and this can be distinguished only with difficulty. When examined in the fresh state or after maceration in Müller's fluid it may be seen distinctly that these nuclei belong to cells (astrocytes) which are characterized by a great number of fine processes extending in all directions, and often branching (Fig. 282, *A*). By proper staining-methods the connection between some of the fibres may be demonstrated also in sections (Fig. 283).

FIG. 283.—Section of a glioma of the cerebrum, with astrocytes (Müller's fluid, hæmatoxylin, Mallory's method.) × 500.

The cells are very similar to normal glia-cells (short-processed or long-processed); but are not infrequently much larger, occasionally more plump, and some may possess two, three, or four nuclei.

The *development of gliomata takes place ordinarily from the supporting cells* of the white and gray substance. A preponderance of cells with a slight development of the cell-processes leads to the formation of *medullary gliomata;* while a more marked formation of processes and of the fibrillated ground-substance gives rise to *hard forms.* As the result of the proliferation of the perivascular connective tissue *gliosarcomata* may be formed.

In gliomata developing in the neighborhood of the ependyma, the *ependymal epithelium,* consisting of cylindrical cells with a basal process, *may also share in the proliferation,* so that the surface of the tumor becomes covered with a layer of ependymal cells. *Epithelial ingrowths resembling gland-ducts* may be formed so that the tumor in part *takes on the character of an epithelial adenoma* (*neuro-epithelioma adenomatosum gliomatosum*). A similar appearance may be produced when, as the result of disturbances of development, misplaced portions of the medullary canal lie within the glioma.

Proliferations arising from the epithelium of the plexus bear the character of epithelial growths.

A **neurogilioma ganglionare** (Fig. 284) is a *tumor of the central nervous system,* composed of hyperplastic *glia-tissue, ganglion-cells,* and *nerve-fibres,* and forms either poorly defined swellings of larger portions of the brain, or circumscribed, nodular enlargements of smaller portions. To the naked eye the structure of the brain may in general appear to be still preserved, though the difference between the cortical and medullary substance is less distinct than normal, and the tissue throughout is white or grayish-white, or spotted gray and white, and at the same time more or less hardened.

The main portions of these masses consist of a more or less thick glia-

tissue containing a certain number of nerve-fibres (d) and ganglion-cells (a, b, c), or cells resembling ganglion-cells, not only in the cortical tissue, but also in the white substance.

Probably all of these formations are to be regarded as the result of disturbances of the embryonal development of the brain—that is, as local malformations of the brain, which are characterized essentially by a *pathological development of neuroglia* (*gliomatosis*) and by a development of part of the neuroblasts, probably also of the spongioblasts, into large *ganglion-like cells* (a) such as are not found normally in the brain.

A *B*

FIG. 294. Section from a nodular neuroglioma ganglionare of the central convolution of the cerebrum (Müller's fluid, Weigert's stain). *A*, Portion of tissue rich in ganglion cells. *B*, Portion of tissue containing nerve-fibres. *C*, jelly-like portion. *a*, Ganglion-cells arranged in groups; *b*, scattered ganglion-cells; *c*, ganglion-cells with two nuclei; *d*, nerve-fibres with medullary sheath; *e*, glia-cells; *f*, blood-vessel. × 275.

The term **glioma** is also applied to certain tumors of the **retina** occurring during childhood. These growths, a certain portion of which are of congenital origin, are evidently to be referred to some disturbance in the development of the retina. They form cellular, soft, white or reddish tumors, the greater part of which consists of small, round or irregular cells poor in protoplasm, resembling the cells of the stratum granulosum. In part they possess smaller or larger processes. These cells are found best preserved in the neighborhood of the blood-vessels, while in other portions of the tumor they often show retrograde changes. The tumor may also contain ganglion-cells, cylindrical cells, and peculiar rosette and ribbon-like cell-formations (Wintersteiner), these latter being regarded as aggregations of rods and cones. Wintersteiner has, therefore, designated the tumor a *neuro-epithelioma*.

The glioma of the retina often shows areas of necrosis in its central portion. In its growth it may break into the retrobulbar space, or forward through the cornea and sclera; it recurs after operation, and gives rise to metastases.

With reference to the origin of neuroglia and ganglion-cells from the ectoderm, various writers class the *different forms of gliomata* with the epithelial tumors. In so far as the ependymal proliferations resembling epitheliomata and adenomata (§§ 118, 119) are concerned, such a classification is justified. The ordinary gliomata, however, show a structure resembling that of the other connective-tissue tumors, so that it is more proper to class them with the latter.

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(*i*) *Amputation Neuroma, Neurofibroma, and the True Neuroma.*

§ 111. The tumors designated **neuromata** occur most frequently on the ends of amputated nerves, where they form more or less prominent swellings, either circumscribed or blending into the surrounding tissue without any clearly defined demarcation. From the conditions of their origin they are known as *amputation-neuromata* (Fig. 285, *b*). The development of these neuromata is to be referred to the changes taking place after the nerves have been severed; during the development of connective tissue in the stump the ends of the axis-cylinders of the proximal portion of the affected nerve divide and grow longitudinally, so that the scar-tissue comes to be penetrated by nerves which at first have no sheaths, but are soon surrounded by medullary sheaths. The mass of nerves penetrating into the granulation tissue may be large, so that the connective tissue after a certain length of time may contain a very rich supply of nerves, which, radiating from the end of the old nerve, extend into the connective tissue in all directions (Fig. 285, *b*). The process is, therefore, an example of a useless *regenerative proliferation of a nerve-stump* exceeding the physiological needs.

As another form of so-called neuromata are classed those growths developing spontaneously, without external cause, along the course of nerves; and which consist essentially of *an increase in the connective tissue of the nerve*, usually of the outer, more rarely of the inner layer of the endoneurium.

At the point of tumor-growth the nerve-bundles become surrounded by a more or less thick layer of connective tissue, which is usually loose, more rarely dense (Fig. 286, *b*, *d*), or the bundles may be split apart into their individual fibres (*c*). Occasionally the perineurium takes part in the proliferation. In the case of large nerve-trunks the epineurium may be affected in association with the endoneurium and perineu-

rium of the individual bundles, although the process is most frequently confined to the endoneurium.

According to their structure these tumors are not true neuromata, but are **neurofibromata** or **fibromata nervorum**. They are usually of *multiple* occurrence, and may extend throughout the entire peripheral nervous system, but are more often limited to a definite area of nerve-distribution. In very rare cases they occur in the nerve-roots and spinal cord. The nodules are sometimes situated along the course of the nerve-trunks, sometimes on the finer branches, most frequently of the cutaneous nerves; and in the skin form more or less numerous, larger or smaller, tumor-nodules, for the greater part of soft consistence, to which the designation **multiple fibromata of the skin** is usually applied. The smallest nodules can be seen only with the microscope; the majority vary in size from that of a pea to that of a hazel-nut. Individual tumors may reach the size of a man's fist, the nerve-fibres being wholly lost sight of in the great mass of connective tissue. Atrophy of the fibres may be caused by the increasing connective tissue, the fibres finally vanishing completely. In addition to the formation of circumscribed nodules there may occur also in the affected area a *diffuse thickening of the nerves from hypertrophy of their connective tissue.* Moreover, with this condition there may be associated a hypertrophic proliferation of the connective tissue of the skin and subcutaneous tissue, leading to *elephantiasis-like thickenings of the skin.*

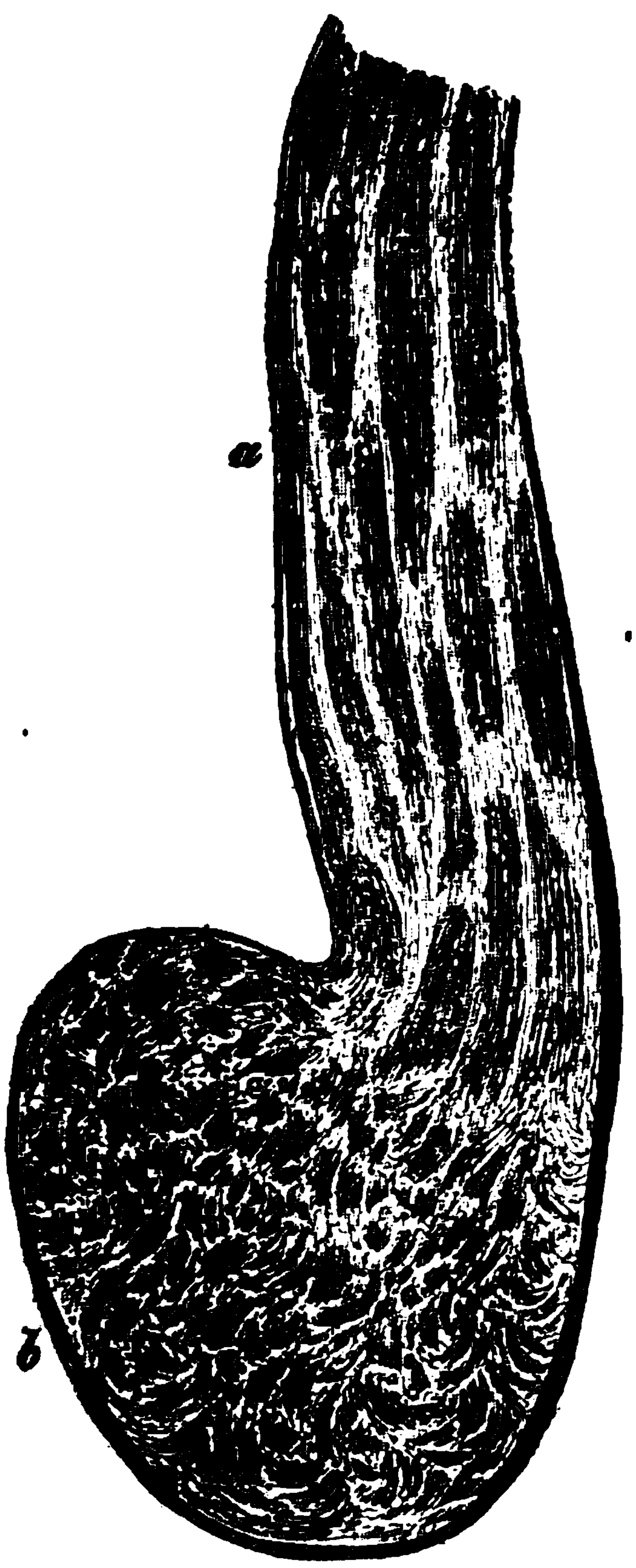

FIG. 285.—Amputation-neuroma of the sciatic nerve (nine years after amputation of the nerve). Longitudinal section. *a*, Nerve; *b*, neuroma. Drawn from a preparation which had been hardened in Müller's fluid. × 3.

A third form of false neuroma is the **cirsoid neuroma** (Bruns) or **plexiform neuroma** (Verneuil), a tumor formation which is characterized by the development in the domain of one or more nerve-branches of a convolution of tendril-like, twisted or interwoven, thickened and nodular nerve-strands (Fig. 287). When examined in detail this formation is also found to depend essentially upon a *fibromatosis of the nerves* (Fig. 286), the proliferation of the endoneurium resulting partly in a diffuse and partly in a nodular thickening of the nerves. In addition, it may be found in such formations that the nerves of the affected area are *lengthened and thereby rendered tortuous*, while at the same time the *nerves are increased in number*, so that the number of the nerves of the skin and subcutaneous tissues is greater than under normal conditions. The condition must, therefore, be regarded as one of true neuroma, a *neuroma verum* associated with a *fibromatosis*. The nerves are for the greater part medullated (*neuroma myelinicum*). It is very difficult to determine to

[illegible]

[illegible] nerves are [illegible] [illegible] [illegible] [illegible] nerve-fibres [illegible] [illegible] nerve [illegible]

Fig. [illegible].—Nerves from an elephantiasis-like cirsoid neuroma of the cheek and lower jaw (Flemming's solution, safranin). a, b, Nerves, the outer layers of whose endoneurium have undergone marked proliferation; the nerve-fibres lie in the axial portion; c, nerve with markedly proliferated endoneurium and separated nerve-fibres; d, thickened nerve with a small strand of nerve-fibres at the left end; e, loose connective tissue, rich in nuclei and containing fat, lying between the nerves. ×7.

romata occur on the head, trunk, and extremities, and give rise usually to *elephantiasis-like disfigurations* of the affected areas.

True neuromata *consisting of nerve-fibres and ganglion cells (neuroma gangliocellulare verum)* are rare tumors; but from the observations of Weichselbaum, Beneke, Busse, Knauss, Schmidt and others, the occurrence of such growths cannot be doubted. They form tumors varying in size from that of a millet seed to that of an apple, and develop particularly in the sympathetic system. In a case described by Knauss there were present multiple nodular neuromata of the skin containing nerve-cells, and it is probable that these growths had their origin in sympathetic [illegible] nerves containing gan-

Fig. [illegible].—Cirsoid neuroma of the sacral region. [illegible]

glion-cells. These tumors consist of connective tissue, non-medullated and medullated nerve-fibres, and ganglion-cells which resemble those of the sympathetic ganglia.

Both the *neurofibroma* and the *true neuroma* are, as regards their origin, to be referred to a *congenital anlage*. They form no metastases, but cases occur in which neurofibromata take on a sarcomatous character and thereby become malignant.

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(*k*) *Sarcoma.*

§ 112. A **sarcoma** *is a connective-tissue tumor whose elements, either because of their number or often because of their size, predominate over the intercellular substance.* Sarcomata are closely related to the undeveloped connective tissues, so that sarcomatous tissue may be compared with *embryonal tissue.*

Sarcomata develop either in previously normal tissue belonging to the connective-tissue group—as, for example, in the skin, subcutaneous tissue, intermuscular connective tissue, periosteum, spinal cord, meninges, connective tissue of the glands, etc.—or in some preëxisting connective-tissue tumor, as a fibroma, myoma, chondroma, hypertrophic

lymphangioma, etc. The transformation of the parent tissue into tumor tissue takes place through the growth and multiplication of the existing cells. The division of the cells takes place chiefly by mitosis, and mitoses are the more abundant the more rapid the growth of the tumor. In addition to typical mitoses there are frequently observed atypical forms, also nuclear fragmentation, and more rarely segmentation.

In their fully developed state sarcomata form more or less sharply circumscribed growths. They may appear in any portion of the body where connective tissue is present; but are found in certain tissues more frequently than in others. Thus, for example, they are found much oftener in the skin, fascia, intermuscular connective tissue, bone-marrow, periosteum, brain, and ovaries, than in the liver, intestines, and lungs.

The development and form of the cells vary greatly in different sarcomata. The intercellular substance is sometimes very scanty, soft, and delicate; at other times more abundant and in character resembling the ground-substance of the mature normal connective-tissue substances.

The amount of the intercellular substance has a marked influence upon the consistence and color of the tumor. The **medullary forms** are soft and very cellular, and poor in intercellular substance; on section they present a marrow-like white or grayish-white surface. The hard, dense forms, on the other hand, are poor in cells and rich in fibrous intercellular substance; they pass by insensible gradations into fibromata. Transition-forms are known as **fibrosarcomata.** The cut surface of a sarcoma presents a nearly uniform appearance, in case retrograde changes or differences in the blood-content do not cause alterations of the same; it is usually uniformly smooth, in the medullary forms milk-white, in the firmer varieties clear grayish-white, somewhat translucent, or more of a clear grayish-red or grayish-brown color. The hard forms are glistening white or yellowish-white.

The development of the blood-vessels varies greatly; sometimes the vessels are very numerous, large, and ectatic (*teleangiectatic sarcoma*). Usually the vessels have walls easily distinguishable from the tumor tissue; but the tumor-cells may also constitute the outer cells of the vessel-wall; and in such a case the cells of the vessel-walls also take part in the growth of the tumor.

Retrograde changes—such as fatty degeneration, mucous degeneration, liquefaction, caseation, necrosis, hæmorrhage, gangrene, ulceration, etc.—are of frequent occurrence in sarcomata.

The sarcomatous tumors may be divided into three classes. The first of these includes the *simple sarcomata*, or sarcomata in the narrower sense—that is, tumors of the type of embryonal connective tissue, showing a more or less uniform distribution of the cells without the formation of distinct groups of cells. The second class includes those sarcomata which show a *special arrangement and grouping of the individual elements*, so that tumor-formations arise which are very similar to the epithelial tumors. The third class is characterized by the appearance of *secondary changes in the cells, in the intercellular substance, and in the blood-vessels*, these changes giving to the tumors concerned a characteristic appearance.

The *etiology of sarcoma* is not a simple one. It occurs more frequently in youth than in old age. Some sarcomata develop even in embryonic life, and the origin of such may be referred to some local malformation. Occasionally trauma appears to be an exciting cause. A parasitic origin has not been demonstrated (see Etiology of Carcinoma). Usually only one primary tumor is formed, but multiple primary sarcomata sometimes

occur, particularly in the skin and bone-marrow. The softer tumors give rise to metastases.

§ 113. The **simple sarcomata** include both soft medullary forms and those of a firmer consistence, which pass by insensible degrees of transition into the *fibrosarcomata* and *fibromata*. According to the character of the cells, several forms may be distinguished.

The **small round-celled sarcomata** are very soft, quickly growing tumors, which develop particularly in the connective tissue of the motor apparatus and supporting framework, and also in the skin, testicles, ovaries, and lymph-glands. On section they appear milky-white, and occasionally present caseous or softened areas. When scraped the cut surface yields a milky fluid. Their structure is very simple; the tumors consist almost wholly of round cells and blood-vessels (Fig. 288, *c*). The cells are small and frail; they possess very little protoplasm, and have spherical or slightly oval, rather large, bladder-shaped nuclei (*c*), which appear to be more highly developed than the nuclei of lymphoid cells.

Between the cells lies a very scanty amount of fibrogranular intercellular substance. The vessels traverse the masses of cells in the form of thin-walled canals. If such a tumor growing in muscle be examined at its periphery it appears as an aggregation of round cells (Fig. 288, *b*, *c*) in the intermuscular connective tissue. Not infrequently lymphoid cells lie near the tumor-cells, the nuclei of the former (*d*) staining more intensely than those of the tumor-cells.

A second form of round-cell sarcoma is designated **lymphosarcoma** or **sarcoma lymphadenoides**; it imitates to a certain extent the struc-

FIG. 288. FIG. 289.

FIG. 288.—Section through the edge of a sarcoma of the intermuscular connective tissue of the cervical muscles (alcohol, carmine). *a*, Transverse section of normal muscle; a_1, transverse section of an atrophic muscle-fibre; *b*, round cells of the sarcoma, between the muscle-fibres; *c*, fully developed tumor; *d*, lymphocytes. × 300.

FIG. 289.—Section from a lymphosarcoma of the nasal mucous membrane (alcohol, carmine). *a*, Reticulum; *b*, cells of the reticulum; *c*, round cells; *a* (at the upper left), blood-vessel with proliferating cells. × 300.

ture of a lymph-gland in that the stroma for the greater part of the round cells consists of a vascular reticulum (Fig. 289, *a*), which in part at least is composed of branching and anastomosing cells (*b*), as may be demonstrated by shaking a small section of the tumor in a test-tube.

According to the amount of reticulum which they possess, the *lymphosarcomata* may be divided into the *soft* and *hard* forms. In the denser

varieties the reticular framework may take on more and more the appearance of ordinary fibrous connective tissue. Especial forms of round-celled sarcoma arising in the bone-marrow are known as myelomata.

Lymphosarcomata arise most frequently in the lymph-glands and the adenoid tissue of the mucous membranes, in the spleen and medias-

FIG. 290.

FIG. 291.

FIG. 290. Section from a fungoid large round-celled sarcoma of the skin of the leg (carmine preparation). × 400.

FIG. 291. Section from a sarcoma of the mamma with cells of different shapes (alcohol, Bismarck-brown). *a*, Connective tissue; *b*, sarcoma tissue; *c*, small cells; *d*, cells with hypertrophic nuclei; *e*, multinuclear cells. × 300.

tinum, but are found also in other places. The tumor-proliferation involves successively a more or less considerable portion of the lymph-adenoid tissues named.

Large round-celled sarcomata, the cells of which are much larger than those of the forms just described, appear in the same places as do the small round-celled variety, and closely resemble the latter. The cells possess an abundant protoplasm and large, bladder-like, oval nuclei (Fig. 290). Many of the cells have two nuclei, some more than two. Between the round cells there lies a reticulated intercellular substance (Fig. 290), as well as spindle-shaped and branched cells, which together form an alveolar network in whose meshes lie the large round epithelial-like cells.

In other forms of large round-celled sarcomata the tumor-cells are very unequal in size (Fig. 291), and at the same time there are mingled with the round cells elongated or irregularly shaped cells, so that the tumor may be called also a **sarcoma with polymorphous cells.** The nuclei likewise vary greatly in size (Fig. 291), and in individual cells *e* may be present in large numbers (multinuclear giant-cells).

The large round-celled sarcomata and the polymorphous-celled variety are on the whole less malignant than the small-celled, but they also give rise to metastases.

Spindle-celled sarcomata belong to the most commonly occurring tumors. As a rule, they are much firmer than the round-celled forms, but soft medullary forms also occur. On section they present ordinarily a grayish-white or yellowish-white, rather translucent surface, which may be more or less reddened according to its vascularity. Medullary tumors whose cells have undergone fatty degeneration may possess a pure white color. In general, these sarcomata are more benign than the round-celled varieties, but their character in this respect varies according to their location and their richness in cells.

According to the size of the cells there may be distinguished **large spindled-celled** and **small spindle-celled sarcomata.** Through the teasing of small pieces of the tumor the cells may in part be isolated, and in this way very long spindles may be obtained (Fig. 292). The cells lie side by side with their flat sides approximated, and are grouped in bundles, which, in sections, are cut partly longitudinally, partly transversely, and partly obliquely—evidence that they are interwoven in different directions.

The arrangement of the spindles in bundles is often very striking; in other cases it is wanting; and the spindles for considerable distances run in the same direction. Sometimes the direction of the spindles is determined by the direction of the blood-vessels—that is, the individual bundles form sheaths about their respective blood-vessels.

Between the spindles there is often but a very scanty intercellular substance, or it may not be possible to demonstrate in sections the presence of such. In other cases it may be more abundant, and show a fibrillar character. The cells in such cases have less protoplasm, so that often it is scarcely possible to demonstrate any protoplasm around the nucleus, and the processes at the poles of the cells seem to spring directly from the nucleus (nuclear fibres). Such varieties are dense and hard. They represent the connecting-link between sarcomata and fibromata, and are designated **fibrosarcomata.**

Sarcomata with polymorphous cells are found also among the spindle-celled forms; and contain spindle-shaped, pyramidal, prismatic, stellate, and very irregular cell-forms (Fig. 293).

Fig. 292. Fig. 293.

Fig. 292.—Spindle-cells from a large spindle-celled sarcoma of the cheek (teased preparation). × 400.

Fig. 293.—Cells from a myelogenous giant-celled sarcoma of the tibia. (Hæmatoxylin.) × 400.

Both in polymorphous- and spindle-celled sarcomata there may be found more or less numerous giant cells (Figs. 291, 293, and 294), so that the designation **giant-celled sarcoma** may be applied to these tumors. They arise particularly from the bones, but they may occur also in other places.

If a sarcoma develops in preëxisting new growths there may be

formed mixed tumors, which are known as **myxosarcoma** (Fig. 252), **chondrosarcoma** (Fig. 257), **myosarcoma**, etc.

FIG. 254.—Giant-celled sarcoma of the upper jaw (Müller's fluid, hæmatoxylin). × 100.

The *lymphosarcoma of the lymph-glands and lymphadenoid apparatus of the spleen and the mucous membrane of the gastrointestinal tract* gives rise to a peculiar disease of these organs, which is characterized by a progressive increase of the lymphadenoid tissue, leading to the formation of extensive nodules. Under these circumstances the characteristic structure of the lymphadenoid apparatus is lost, and the newly-formed tissue shows a marked departure from the structure of typical lymphadenoid tissue—namely, a fibrous thickening of the reticulum or the formation of giant-cells. Since similar growths occur also in other organs, such as the liver, the disease cannot be looked upon as a pure hypertrophy of lymphadenoid tissue, but as a tumor-formation with the production of lymphoid cells. It is also possible that it is an infectious disease. Likewise the condition known as *sarcomatosis cutis*, which is characterized by the formation of numerous round-celled nodules in the skin, is to be classed with it.

The *myelomata of the bones*, occurring as multiple nodules either concealed in the bones or projecting from their surface, demand especial consideration. According to recent investigations (*Sternberg, Ribbert, Hoffmann*) they are composed of cells corresponding either to the myelocytes, lymphocytes, erythroblasts, or plasma-cells.

The common characteristic of the *lymphosarcoma* and *myeloma* is that, aside from the reticular framework, they consist essentially of *derivatives of free mesenchymal cells*, and are thereby differentiated from the ordinary sarcomata that arise through the proliferation of fixed tissue-cells. They form, therefore, an *especial group* among the connective-tissue tumors, but the investigations so far carried out are not sufficient to fix their position more definitely.

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See also §§ 114–116

§ 114. **Sarcomata which present an organoid structure** appear in those forms known as **alveolar** and **tubular sarcomata.** These are connective-tissue tumors in which the cellular elements, especially the larger cells, are arranged in groups, so that it is possible to distinguish a *vascular connective-tissue stroma* and *strands* or *nests of cells.* According to their genesis, these growths may be divided into two types: *lymphangiosarcoma* and *hæmangiosarcoma.* There are, however, also alveolar sarcomata which possess stroma and cell-nests, but which, in so far as their development is concerned, cannot be included with the above-named types.

The **lymphangiosarcomata** are tumors which arise from a *proliferation of the endothelium of the lymph-vessels and lymph-spaces.* They may accordingly be designated as **lymphangioendotheliomata** or as *endotheliomata in the narrower sense.* They may develop either in previously normal tissue, or in preëxisting tumor-like formations, such as the hypertrophic lymphangioma in particular (pigmented moles and warts, see § 108), and also from myxochondromata. The first occur particularly in the meninges of the brain, and in the serous membranes of the great body-cavities; but may develop also in other organs; the second are found chiefly in the skin; while those arising from myxochondromata develop in the mixed tumors of the salivary glands, palate, and orbit.

The *endotheliomata of the inner meninges of the brain and spinal cord* occur partly as nodular growths and partly as flattened proliferations; they develop through the transformation of the flattened endothelium, which covers the connective-tissue network of the subarachnoideal tissue and pia, into cubical or even cylindrical cells (Fig. 295, *d*, *e*). In consequence, the new-growth at first presents the appearance of *gland-like formations;* in the event of a more active proliferation solid *nests of cells* are formed. Inasmuch as the pia is continued as a lymph-sheath around the cerebral vessels, there are formed around the latter strands of large epithelial-like cells (Fig. 295, *f*, *g*, *h*).

The *endothelioma of the dura mater* arises through a proliferation of the endothelium of the lymph-vessels, and leads, through the filling up of the latter with large cells, to the formation of anastomosing cords of cells (Fig. 296, *c*, *d*, *e*), which in some places may still contain a lumen.

The *endotheliomata of the pleura or of the peritoneum* appear usually as flattened thickenings of the affected membrane, but scattered nodular elevations may occur throughout the areas of thickening. These growths

b

FIG. 295.—Section through an endothelioma of the pia mater and cerebral cortex, diffusely spread over the surface of the brain and spinal cord (Müller's fluid, hæmatoxylin). *a*, Superficial pia; *b*, pia in a sulcus; *c*, cortex; *d*, *e*, endothelial proliferations in the pia sheaths of the cortical vessels; *f*, *g*, *h*, endothelial proliferations in the pia sheaths of the cortical vessels; *i*, longitudinal section through a vein. × 25.

are characterized by cords of large cells (Fig. 297, *b*), which, corresponding to the course of the lymph-vessels, traverse the hypertrophic and proliferating tissue of the serosa.

The *endothelioma of the mammary gland* is a rare tumor, which develops in the form of nodules, and takes its origin from a proliferation of the endothelium of the lymph-vessels and lymph-spaces (Fig. 298, *b*, *c*), and gives rise to the formation of large cords of cells (*c*) or of smaller cell-nests. The proliferating cells are characterized by a great variation in the size, character, and form of the nucleus and cell-body.

The *endothelioma of the skin*, which arises from the hypertrophic lymphangioma (warts and pigmented moles), resembles these in its general structure, and possesses also cell-nests of varying size (Fig. 277). Further, there also occur endotheliomata of the skin, which do not arise from warts, and may develop in great numbers (Spiegler, Mulert).

The *endothelial proliferations which arise in myxomata and myxochondromata* form cords of cells of different shapes (Fig. 252, *b*); but it should

be noted that in these cases similar proliferations may also arise from the blood-vessels (Fig. 302. *c, d*), so that it is often impossible to decide as to the nature of the cell-strands.

The alveolar, tubular, or plexiform structure of the endothelioma is well marked only in the first stages of the tumor, and usually disappears

FIG. 296.—Endothelioma duræ matris (Müller's fluid, hæmatoxylin). *a*, Connective-tissue stroma; *b*, small-celled focus; *c*, groups and strands of cells arising from the proliferation of lymph-vessel endothelium, *d*, endothelial cell-strand with a lumen; *e*, area of fatty degeneration in nest of endothelial cells; *f*, strand of cells, passing gradually, on the right, into the surrounding connective tissue. × 25.

in part with the advancing growth of the tumor. This is due, on the one hand, to the fact that the endothelial proliferation extends, without

FIG. 297.—Endothelioma of the pleura (alcohol, hæmatoxylin). *a*, Proliferated and thickened pleural connective tissue; *b*, cell-strands. × 100.

sharp limits, into the neighboring connective tissue (Fig. 296, *f*); and, on the other hand, to the circumstance that the connective-tissue cells

take on a proliferative activity similar to that of the endothelium, so that there is formed a diffuse, cellular new growth of the character of

FIG. 298.—Endothelioma of the mammary gland (alcohol, hæmatoxylin, eosin). *a*, Connective tissue; *b*, enlarged cells in the connective-tissue spaces; *c*, strands of cells; *d*, diffuse cell-proliferation. × 300.

an ordinary sarcoma (Fig. 298, *d*). Accordingly, the endotheliomata cannot be sharply distinguished from the sarcomata, and may become transformed into the latter.

The similarity in structure between endotheliomata and carcinomata raises the question whether it would not be expedient to class the former as *endothelial cancers*. The structure of these tumors would certainly justify such a classification, but I consider it better to avoid the use of this term. In the first place, the term endothelioma is in general use and is entirely appropriate, and the introduction of the term endothelial cancer would easily give rise to confusion: by the term cancer in general is understood an epithelial tumor, and it does not seem expedient to introduce two types of cancer—an epithelial and an endothelial.

I have classed as endotheliomata those tumors of the serous membranes which are characterized by the formation of cell-cords in the lymph channels, on the assumption that these cords of cells arise from the endothelium of the lymph-vessels and lymph spaces. I must admit, however, that I do not consider this assumption as absolutely proved, in spite of the concurring definite statements of a number of authors (see *Glockner*). The possibility of their development from the epithelium of the serosa is not excluded (*Benda*), and if such an origin could be proved, the question would arise whether it would not be better to class these tumors with the carcinomata, since the corresponding tumors of the kidneys and ovaries, whose gland-cells arise from peritoneal epithelium, are classed with the epithelial tumors.

According to investigations by *M. B. Schmidt*, the cellular elements of the sarcomata of the dura mater, as well as of the psammomata (§ 116), that for the chief part are located in the neighborhood of the dural sinus, arise from *endothelial cells of the arachnoid* that under physiological conditions are pushed into the tissue of the dura, in part by the ingrowing Pacchionian bodies, and in part as independent cell-plugs from the smooth surface of the arachnoid.

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See also §§ 118 and 115.

§ 115. The **hæmangiosarcomata** represent a group of organoid sarcomata, in which the walls of the blood-vessels and their surrounding

FIG. 298.—Blood-vessel endothelioma of the kidney (formalin, hæmatoxylin, eosin). *a*, Vessels filled with blood; *b*, vessels filled with proliferated endothelial cells. × 300.

tissue take an especial part in the building-up of the tumors, and constitute a characteristic feature of their structure.

One form of hæmangiosarcoma is the **blood-vessel-endothelioma** or **hæmangioendothelioma,** a tumor which arises, either from preëxisting

FIG. 300.—Section through a nodular angiosarcoma of the thyroid (Flemming's solution, safranin). *a*, Transversely cut vessels; *b*, perivascular cylinders of cells cut transversely and showing numerous mitoses; *c*, granular masses, with scattered cells, between the cell-cylinders. × 73.

blood-vessels or those newly formed in hæmangiomata, through a more active development and proliferation of the endothelium giving rise to

FIG. 301.—Angiosarcoma of the testis (Müller's fluid, hæmatoxylin, eosin). *a*, Perivascular masses of closely packed cells; *b*, areas poor in cells; *c*, hyaline lumps; *d*, hyaline masses containing blood; *e*, seminiferous tubules; *f*, large vein. × 80.

blood-vessel spaces lined with cubical or cylindrical endothelium (Fig. 299, *a*), or to canals completely filled with such cells (*b*). According to the number of blood-containing vessels the tumor is either dark-red, pale, grayish-white or yellowish-white. The endothelial cells, according to the stage of development, may contain glycogen or fat or both.

A second form of hæmangiosarcoma, the **hæmangiosarcoma** in a narrow sense (occasionally also called *perithelioma*), arises through the proliferation of the tissue of the outer layers of the blood-vessel walls and their immediate surroundings, so that the vessel-lumina are surrounded by a more or less thick mantle of cells (Fig. 300, *b*).

In typical cases the tumor-tissue consists almost wholly of a confused tangle of blood-vessels (Fig. 300, *a*), whose walls are surrounded by a thick layer of cells, which often reach to the endothelium. The thick-walled tubes of cells sometimes run an isolated course, and at other times anastomose, so that variously formed twistings and interweavings result

FIG. 302.—Chondrofibroma of the parotid with angiosarcoma (Müller's fluid, hæmatoxylin, eosin). *a*, Areas of cartilage; *b*, dense sarcoma tissue; *c*, blood-vessel; *d*, cell-strands arising from blood-vessels, and in part containing a hyaline substance. × 80.

(*plexiform angiosarcoma*). The tissue lying between the cell-strands is the remains of the original tissue (Fig. 301, *b*), and may still contain characteristic tissue-formations, as, for example, glands (*e*).

Should a more active proliferation of the perivascular mantle of cells occur, and if these become confluent with each other (Fig. 301) the tumor passes over into an ordinary sarcoma. This change almost invariably occurs in the larger tumors of this kind.

Hæmangiosarcomata occur in the most varied organs: testicles, kidneys, salivary glands, bones, brain, mamma, thyroid, skin, carotid gland, coccygeal gland, ovaries, and liver. In the last-named organs they are rare. Both forms may so occur that the tumor throughout bears the char-

acter of a hæmangiosarcoma; but it also happens that such proliferations of the vessels form only a single feature of other tumors (Figs. 302, *c*, *d*; 311, *d*); and though this feature indeed gives character to individual portions, it is, on the whole, overshadowed by other features of the growth—as, for example, a fibro-cellular tissue, cartilage (Fig. 302, *a*, *b*) or myxomatous tissue (Fig. 311, *a*).

Lymphangiosarcomata and hæmangiosarcomata cannot always be sharply differentiated from each other, and tumors occur to which both designations may be applied with propriety. The perivascular development of the endothelial proliferation within the brain in endothelioma of the pia (Fig. 295, *f*, *g*, *h*) would justify also the application of the term hæmangiosarcoma.

FIG. 303.—Alveolar melanotic sarcoma of the skin (alcohol, hæmatoxylin). *a*, Mononuclear, a_1, multinuclear sarcoma cells of epithelial character; *b*, pigment-containing cells; *c*, stroma with blood-vessels and pigment. × 300.

If in a lymphangiosarcoma of the skin there is such a rapid development of the cell-nests that the space between the vessels becomes wholly filled with cells, so that the framework of the tumor comes to consist only of blood-vessels (Fig. 303), it becomes an open question as to whether the tumor should be called a lymphangioendothelioma or a hæmangiosarcoma.

Borst, in his work on tumors, has entirely separated the *endotheliomata* (lymphangio- and hæmangio-endothelioma) from the sarcomata, and has attempted to class them as an especial form of neoplasm. In so far as typical microscopical pictures are concerned, such a separation is indeed possible, but the endotheliomata in general do not show in all portions so typical a structure that they can be distinguished from ordinary sarcomata. Further, it is by no means determined that endothelial cells of the lymph-spaces and vessels do not take part in the formation of sarcomata. It seems to me, therefore, better to consider the endotheliomata as an especial form of sarcoma in which the structure of the tumor still permits us to see that undoubted endothelial cells give rise to the cell-masses.

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See also §§ 114 and 116.

§ 116. **Sarcomata which acquire a peculiar character through especial products of the cells or through changes in their ground-substance** are to be found both among the simple and the organoid forms. The chief types belonging in this class are the melanosarcoma, chloroma, osteosarcoma, osteoid sarcoma, the petrifying sarcoma, psammoma, and the sarcomata containing hyaline formations.

Melanosarcomata occur in tissues which contain pigmented connective-tissue cells—*chromatophores*. They develop most frequently in the choroid of the eye and in the skin. In the latter case they arise chiefly from pigmented moles and lentigines. They belong to the malignant sarcomata, grow into the neighboring tissues, and give rise to metastases. The fully developed tumor is in whole or in part smoky gray to black or brownish-black, the color being due to the presence of round, angular, fusiform, and branched cells, which are filled with yellowish-brown pig-

FIG. 204.—Melanotic sarcoma of the skin (alcohol, carmine, eosin). *a*, Sarcoma tissue rich in cells; *b*, cell-nests; *c*, pigment-cells; *d*, blood-vessels with hyaline walls. × 300.

ment granules (Figs. 304, *b*, *e*; 305, *c*), or are stained a diffuse yellow. In the alveolar forms both the large cell-nests, as well as the smaller cells of the supporting framework, may contain pigment. It is often

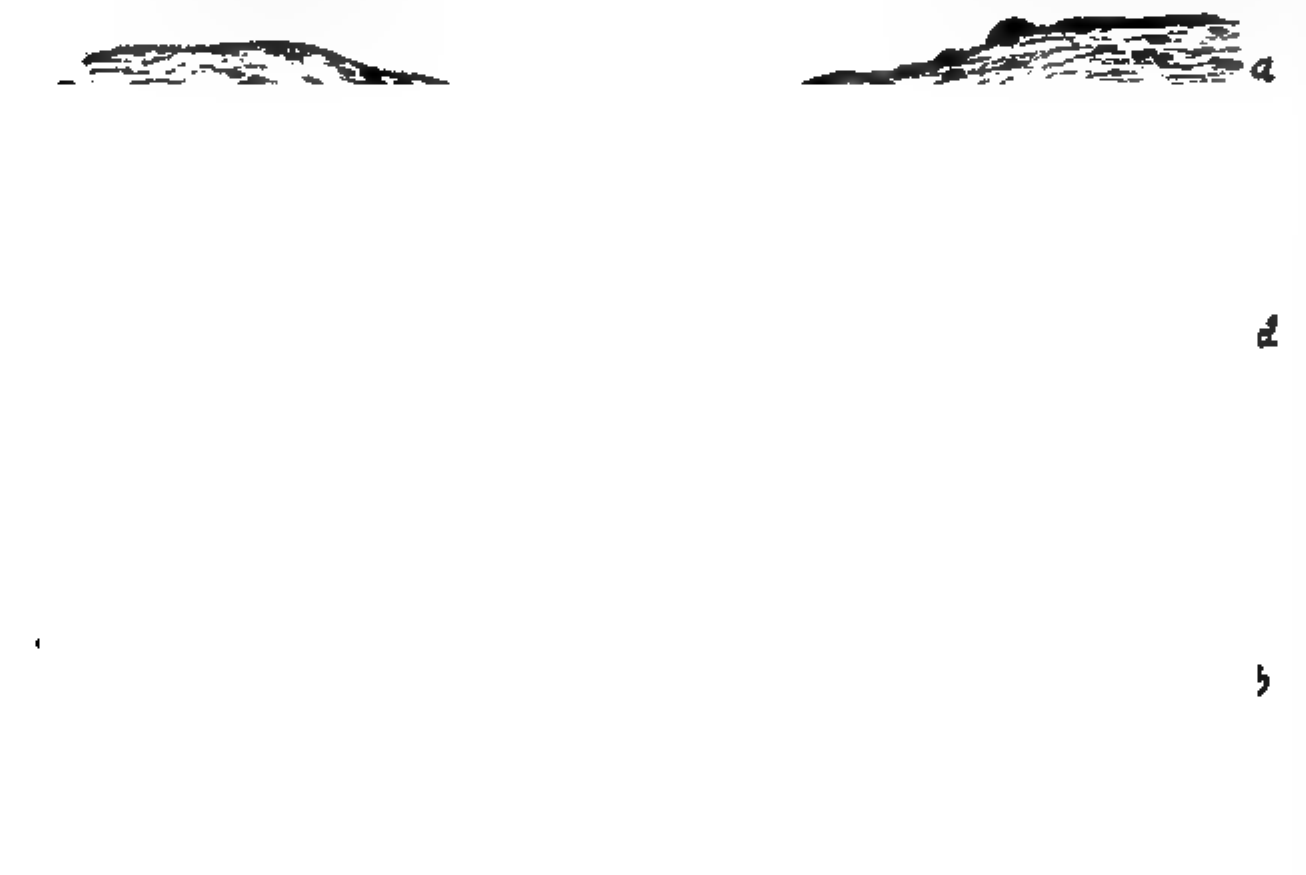

FIG. 305.—Metastasis of a melanotic sarcoma of the skin in the mesentery of the small intestine (formalin, alum-carmine). *a*, Peritoneum; *b*, fat tissue; *c*, sarcoma nodule; *d*, isolated chromatophores. × 98.

FIG. 306.—Endosteal osteosarcoma of the humerus. (Formalin, nitric acid, hematoxylin and eosin.) *a*, Old bony trabeculæ of the spongiosa; *b*, sarcomatous proliferation arising from the endosteum; *c*, c_1, new-formed bone; *d*, blood-vessel. × 80.

especially abundant in the neighborhood of the blood-vessels (Figs. 303, *c*; 304, *d*); but this pigment is not hæmosiderin.

The metastases are likewise more or less pigmented (Fig. 305); and the smallest ones may consist essentially of pigmented cells (*c*, *d*). Cases occur in which numerous organs, the skin, muscles, pia, serous mem-

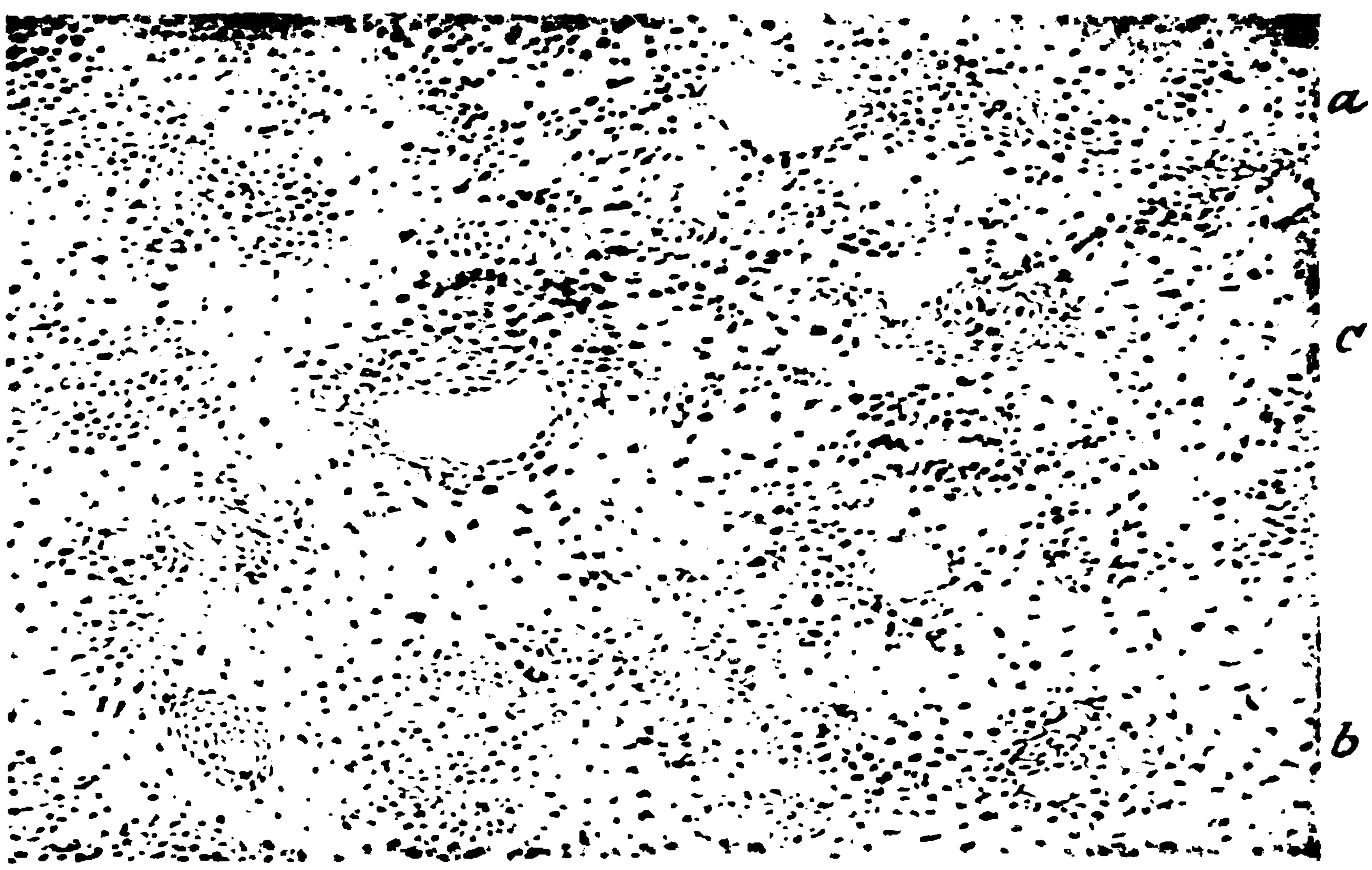

FIG. 307.—Sarcoma ossificans. (Formalin, nitric acid, hæmatoxylin, and picrofuchsin.) *a*, Sarcoma tissue; *b*, new-formed bone; *c*, areas of transition. × 40.

branes and adipose tissue (Fig. 305) are spotted black through the formation of innumerable metastases.

Chloromata are tumors the cut surface of which presents a light-green color which on exposure to the air takes on a dirty appearance.

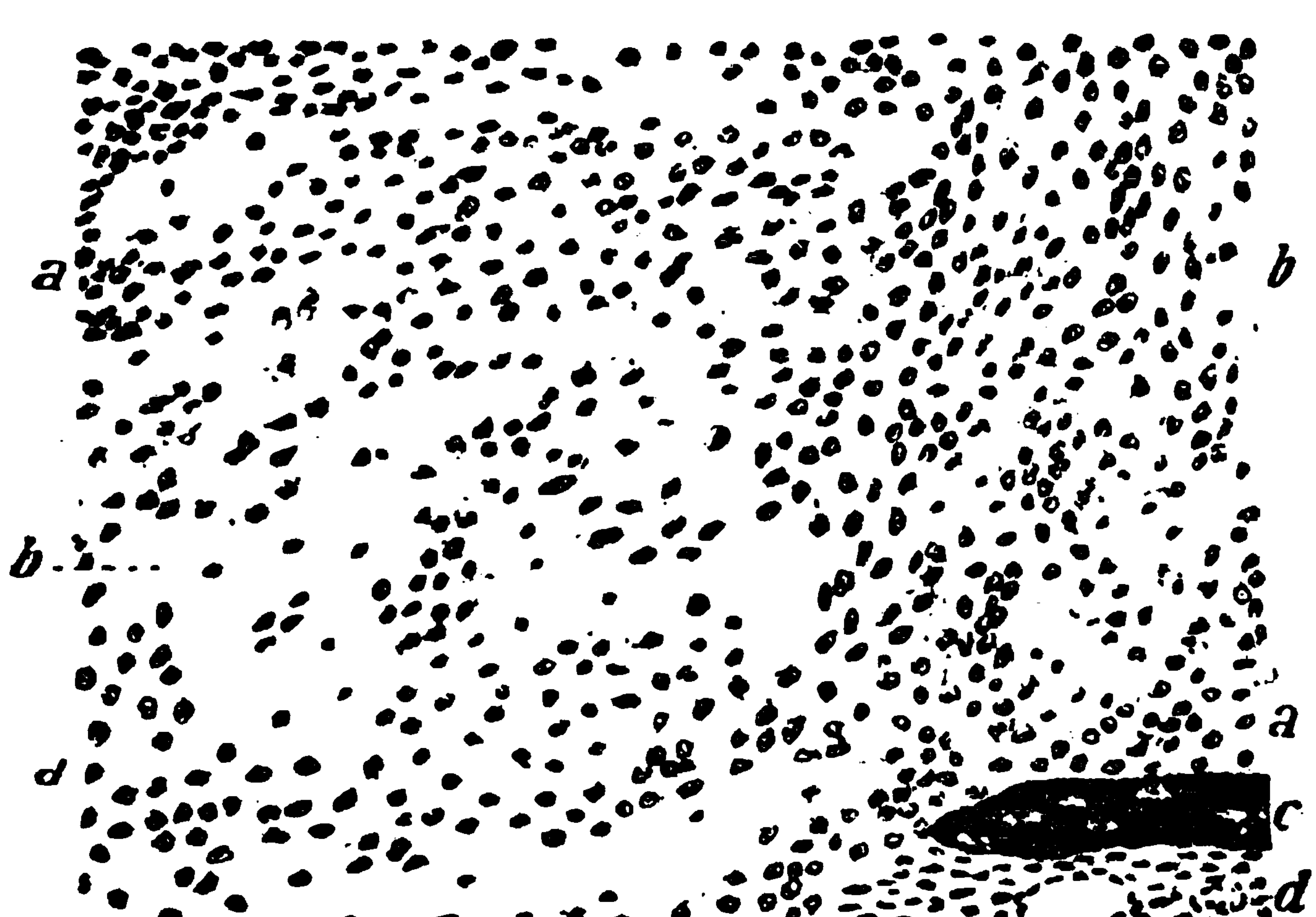

FIG. 308.—Osteoid sarcoma of the ethmoid bone (Müller's fluid, hæmatoxylin, eosin). *a*, Sarcoma tissue; *b*, osteoid tissue; *c* old bone-trabeculæ; *d*, vascular fibrous tissue. × 45.

They develop most frequently from the periosteum of the cranium; and consist of tissue made up of round cells and a reticular stroma.

FIG. 309.—Petrifying large-celled sarcoma of the tibia (Müller's fluid, hæmatoxylin, eosin). *a*, Polymorphous tumor-cells; *b*, alveolar stroma; *c*, trabeculæ of stroma containing small calcareous concretions; *d*, petrifying trabeculæ of the stroma. × 200.

They may, therefore, be classed with the lymphosarcomata. They may be associated with a lymphæmia. Recent studies (Warthin, Klein and Steinhaus, etc.) show that chloromata are primary tumors of the bone-marrow, arising from the parent-cells of the white-cells. Some consist chiefly of myelocytes, either neutrophile or eosinophile, while others are composed of cells resembling-lymphocytes. There is usually an associated leukæmic condition of the blood.

According to Chiari and Gruber, the green color is due to the presence in the cells of small shining spherules which give the microchemical reactions of fat. In harmony with this view is the fact that the color disappears in alcohol. On the other hand, von Recklinghausen holds that the color is a property of the parenchyma and that no morphological elements are the carriers of the color.

Osteosarcomata or **ossifying sarcomata** occur chiefly in connection with the skeleton and are characterized by the new-formation of bone within sarcomatous tissue. The new bone arises at times from a thick homogeneous ground-substance (c, c_1) formed between the tumor-cells (Fig. 306, *b*) which is either connected (c_1) with the old bony trabeculæ (*a*) or arises independently (*c*), or at other times from a coarsely fibrillated connective tissue (Fig. 307, *c*) which gradually becomes condensed (*b*) and, taking up lime-salts, is transformed into bone.

FIG. 310.—Section from a psammoma of the dura mater (alcohol, picric acid, hæmatoxylin, eosin). *a*, Hyaline nucleated spherule inclosing calcareous concretion; *b*, calcareous concretion with hyaline non-nucleated border, inclosed in fibrous connective tissue; *c*, calcareous concretion surrounded by hyaline connective tissue; *d*, spicule of lime in the connective tissue; *e*, spicule with three concretions. × 180.

Osteoid sarcomata develop in the endosteum and periosteum, and

are characterized by a thickening of the ground-substance in certain areas, so that there are formed *trabeculæ of osteoid tissue* (Fig. 308, *b*). Such tumors are closely related to the osteosarcomata, but differ from them in the absence of deposits of lime-salts.

Petrifying sarcomata likewise occur most frequently in connection with the skeleton, and are characterized by the development between the tumor-cells of trabeculæ of a delicate ground-substance (Fig. 309, *c*), through the *calcification* (*d*) of which the tumor tissue becomes hardened, although no typical bone is formed.

Psammomata or *sand tumors* (acervulomata) are sarcomata or fibrosarcomata of the dura, inner meninges, or pineal gland, which contain *concretions of lime-salts* in greater or less abundance. Some of these concretions are similar in structure to the normal brain-sand, the basis of their formation being concentric layers of cells which have undergone hyaline degeneration (Fig. 310, *a*, *b*, *c*). Occasionally the chalky spherules lie inside of individual cells and represent hyaline products of the cells which have later become calcified. Others are more of the nature of spicules (*d*), and arise through the deposit of lime-salts in connective tissue or blood-vessels which have undergone hyaline degeneration.

FIG. 311.—Myxo-angiosarcoma of the parotid, with hyaline formations (Müller's fluid, hæmatoxylin, eosin). *a*, Myxomatous tissue; *b*, cell-strands including hyaline spherules; *c*, hyaline spherules in myxomatous tissue; *d*, blood-vessels with proliferating endothelium and hyaline spherules. × 90.

Psammomata usually form round nodules, and may be of multiple occurrence.

Sarcomata with hyaline formations (the myxosarcomata excepted) arise as follows: *Either the cells form hyaline products, or they themselves become converted into such, or the fully developed connective tissue and the blood-vessels undergo hyaline degeneration.* These changes may take place in simple sarcomata as well as in endotheliomata and hæmangiosarcomata;

but occur much more frequently in the last-named tumor-forms (Figs. 307, *b*; 302, *d*; 311). The hyaline masses may form spherules, or club-like forms, or cords, or net-like or cactus-like figures. They push the cells apart, and often reduce them to narrow strands. Billroth has designated such tumors as *cylindromata*. In endotheliomata the hyaline degeneration may be associated with the formation of *laminated masses of flattened cells like the layers of an onion*, around a nucleus.

Hyaline degeneration of the vessel-walls and of the connective-tissue bundles results in a thickening of the same (Fig. 304, *d*), sometimes uniformly and sometimes irregularly distributed. *Hyaline products of cells* have a tendency to assume a spherical form (Figs. 297, *b*; 302, *d*; 311, *c*, *d*). The disintegration of larger cell-masses with hyaline change leads to the extensive formation of hyaline spherules, strands, or branching structures.

If, in endotheliomata and angiosarcomata, the cord-like masses of cells which have been formed within the lymph- or blood-vessels become converted into hyaline masses, there will be produced formations which greatly resemble glands containing colloid (Fig. 311, *d*); and which have often been mistaken for such.

Ribbert regards the melanosarcoma as an especial form of tumor arising from the chromatophores, and would for this reason separate it from the sarcomata as an individual tumor-type. It is to be noted, however, that in the development of the melanotic sarcoma other cells besides the chromatophores take on proliferative activity; so that melanotic sarcomata can be regarded only as sarcomata in whose development certain cells, which possess the power to form pigment, have taken part.

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See also §§ 114 and 115.

2. The Epithelial Tumors.

(*a*) *General Remarks.*

§ 117. The **epithelial tumors** are new growths, in the formation of which both vascular connective tissue and epithelial cells—that is, cells which are derived from either superficial or glandular epithelium—take part. The distribution of epithelium and connective tissue follows in general the normal arrangement of these tissues, the connective tissue either forming a basement structure whose surface is covered with epithelium (skin and mucous membranes), or forming a network or stroma, in the meshes of which the epithelial cells are disposed (glands). The imitation of the first-named structure leads to the formation of **papillary**

Fig. 312.—Papillary epithelioma or ichthyotic wart of the skin (Müller's fluid, hæmatoxylin, eosin). *a*, Corium; *b*, enlarged papillary body; *c*, laminated horny layer. × 25.

new-growths; that of the second, to the formation of more or less sharply circumscribed **nodules** or to **extensive superficial thickenings of tissue.**

According to the physical characteristics and grouping of the epithelial cells, as well as the clinical behavior of these tumors, epithelial new-growths may be divided into two groups; one group including the **papillary epitheliomata, adenomata,** and **cystadenomata**; the other the **carcinomata** and **cystocarcinomata.** The first group is characterized clinically by the benign character of the growths, *which are sharply circumscribed* and form *no metastases.* The second group, on the other hand, includes the malignant new-growths, *which grow by infiltration and give rise to metastases.* The two groups, however, are not sharply separated from one another, as papillary epitheliomata and adenomata may, through changes in the mode of reproduction and the manner of spreading of the epithelial cells, become changed into carcinomata.

By various German authors all epithelial tumors are called *epitheliomata*, the benign forms as well as the malignant. The French apply the term epithelioma to carcinoma, but not to the benign papillary epitheliomata, adenomata, and adenocystomata. The extension of the designation epithelioma to all epithelial tumors may be justified from the scientific side, but is not practical. The name carcinoma is so universally used that it would not be easily given up. If we apply the term epithelioma to both carcinoma and adenoma, we are deprived of any especial designation for the benign epithelial tumors, and we are, therefore, forced to use various modifying terms in order to express clearly the tumor-form meant. The adenoma, for example, would have to be designated as epithelioma adenomatosum benignum.

(b) *Papillary Epithelioma, Adenoma, and Cystadenoma.*

§ 118. A **papillary epithelioma** is a new-growth which is composed of a framework of connective-tissue papillæ covered with epithelial cells. In structure it is therefore similar to the papillæ of the skin; but the

FIG. 313.—Senile horny wart of forehead, from a woman eighty-four years of age (alcohol, hæmatoxylin, eosin). *a*, Corium; *b*, epithelium; *c*, atrophic sebaceous glands with development of horny epithelium in their ducts; *d*, hypertrophic horny layers; *e*, enlarged papillæ. × 15.

papillæ of the new growth are as a rule higher and often branched, and the epithelial covering thicker.

The papillary epithelioma of the skin occurs in the form of *warty protuberances*, which consist of slender papillæ (Fig. 312) covered with epithelium, the superficial layers of which show marked cornification (*ichthyotic warts* and *horny warts*). These warts may, like the fleshy warts (see § 108), appear during childhood (*ichthyotic warts*) as well as in old age (*verruca senilis*). The first-named form represents a local malformation of the skin (Fig. 312); while the last-named is due to a pathological proliferation and cornification of the epithelium (Fig. 313, *c*, *d*) followed by an outgrowth of the papillæ at the periphery. An excessive cornification of the epithelium over hypertrophic papillæ, giving rise to cylindrical or conical masses of horny cells in which the horny layers lie at right angles to the surface of the skin, leads to the formation of a *cutaneous horn or cornu cutaneum* (Figs. 134 and 135).

Papillary epitheliomata of the mucous membranes occur either in the form of warty, nodular formations (Fig. 314, *e*, *f*), or in that of long, slender, papillary excrescences (Fig. 315, *a*), which, springing from a narrow base, are often repeatedly branched. The former variety is found especially frequently in the lar-

FIG. 314.

FIG. 315.

FIG. 314.—Papillary epithelioma of the larynx. *a*, Epiglottis; *b*, ossified cricoid cartilage; *c*, thyroid cartilage; *d*, trachea; *e*, *f*, papillary proliferations. Natural size.

FIG. 315.—Papillary epithelioma of the urinary bladder. *a*, Epithelioma; *b*, *c*, enlarged prostate; *d*, thickened bladder-wall. Five-sixths natural size.

ynx, more rarely in the nose and urinary bladder; the latter most frequently in the urinary bladder and pelvis of the kidney, vaginal portion of the uterus, and more rarely in the ureters, gall-bladder, and biliary passages.

In both cases the excrescences are formed of slender, connective-tissue

vascular papillæ (Fig. 316) which contain blood-vessels, and are covered by a thick layer of epithelium. The character of the epithelium corresponds in general to that of the part in which the growth occurs, but papillomata covered with stratified squamous cells are sometimes seen in regions which normally possess cylindrical epithelium (nose, trachea).

Papillary epitheliomata in **dilatation-cysts**, which are also called **papillary cystomata**, occur most frequently in cysts of the ovary and in cysts of the ducts of the mammary gland, more rarely in *atheromata* (dermoids) of the skin. Within the cyst are formed small, warty elevations or cauliflower-like tumors, which under certain conditions may fill the entire cyst-cavity. Their structure corresponds to that of the similar excrescences in papillary adenocystomata (see § 120), or the papillary epitheliomata of the skin and mucous membranes.

Papillary epitheliomata of the surface of the ovary appear in forms similar to those of the urinary bladder, but are rare. **Papillary epitheliomata of the cerebral ventricles** take their rise in part from the telæ choroideæ.

Fig. 316.—Papillary epithelioma of the urinary bladder (alcohol, hæmatoxylin, eosin). × 25.

It is difficult to draw a sharp line between **papillary epitheliomata** and other formations. In particular do those inflammatory proliferations of the skin and mucous membranes—the **pointed condylomata**—which develop especially upon the external genitals under the influence of chronic irritations (compare Fig. 234), so closely resemble the epitheliomata that their inflammatory origin forms the only point of difference. If the connective-tissue framework of the papillary outgrowths is developed to a greater extent than the epithelium, the tumor may be classed with the **papillary fibromata**, and it becomes a question of individual standpoint as to which designation shall be employed. Intermediate forms can be designated as **papillary fibroepitheliomata**. Finally, the benign papillary epitheliomata may pass over into **carcinomata**, either through the growth of the epithelium at the base of the papillæ into the underlying connective tissue, or through the extension of the proliferating surface epithelium upon neighboring organs (as in the case of the papillary epitheliomata of the ovary).

Among the epitheliomata may be classed those formations known as **cholesteatomata** or **pearl tumors**, which in part are caused by inflammation, and in part represent misplaced embryonal tissue. The most striking characteristic of the cholesteatoma is the formation of glistening white pearls, which consist of thin, scale-like epithelial cells pressed closely together, and often inclose cholesterin. These tumors are found

most frequently in the descending urinary passages, the cavities of the middle ear, and the pia of the brain; very rarely in that of the spinal cord.

Pathological cornifications, with the formation of glistening white scales and pearls, occur in the *urinary passages*, particularly in the course of chronic inflammations. In the *tympanic cavity, mastoid antrum*, and *external auditory canal*, the cholesteatomata appear as yellowish-white or bluish-white nodules, varying in size from that of a cherry-stone to that of an egg, and presenting an onion-like laminated structure. Through their pressure upon the neighboring bone they may cause its disappearance. They arise as a product of squamous epithelium which has penetrated from the external ear through openings in the ear-drum into the cavities of the middle ear and has replaced the cylindrical epithelium, and under especial conditions (chronic inflammations) produces the formations above described. It is probable that in rare cases they arise from epidermoidal cells which during the period of embryonic development have found their way into the cavities in question.

The *intracranial cholesteatomata* are found at the base of the brain (very rarely in the spinal canal), in the region of the olfactory lobe, tuber cinereum, corpus callosum, in the choroid plexus, in the pons, medulla oblongata, and cerebellum. In these regions the cholesteatomata appear on the surface as silk-like, shining nodules of varying size which extend more or less deeply into the brain-substance. The nodules are single, but cholesteatoma-masses may become separated from the chief nodule and displaced into the neighboring tissue. According to *Boström*, it is always possible to demonstrate, at some point, a connection between the pia and the cholesteatoma, where the scales composing the cholesteatoma take their origin from a cell-layer lying upon the vascular connective tissue, the cells of this layer throughout bearing the character of epidermoidal cells. The cholesteatomata of the pia may therefore be designated as *epitheliomata* or as *epidermoids* (*Boström*); and their origin may be explained by the assumption that in the early period of development epidermal germs are misplaced into the anlage of the pia. According to *Boström*, this takes place in the time between the closure of the medullary canal and the separation (by a process of constriction) of the secondary vesicle of the fore-brain from the fore-brain or the 'tween-brain, and the separation of the after-brain vesicle from the hind-brain (fourth to fifth week). These epidermoids may therefore be classed with the teratoid tumors (see Teratoma).

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§ 119. The **adenomata** are usually *nodular tumors* with sharply defined borders; and are situated within glands, or in the skin or mucous membranes. In the latter situations they not infrequently appear in the form of polypi elevated above the surface. They may occur also in the

Fig. 317.—Adenoma tubulare (glandular polyp) of the intestine (alcohol, alum-carmine). a, Transverse section, b, longitudinal section of gland-tubules; c, stroma rich in cells. × 90.

form of papillary proliferations (Fig. 241). The absence of any tendency to grow by infiltration or to produce metastases stamps these growths as *benign tumors.*

Fig. 318.—Adenoma tubulare of the stomach in an atrophic mucosa (formalin, alcohol, hæmatoxylin, eosin). a, Mucosa; b, muscularis mucosæ; c, submucosa; d, muscularis; e, serosa; f, adenoma. × 14.

The chief characteristic of the adenoma is the *formation of new glands*, which depart more or less from the typical glands of the affected organ. According to their structure adenomata may be classed as *tubular* or *acinous;* but these two forms cannot be sharply separated, the one from

FIG. 319.—Adenoma mammæ tubulare (alcohol, alum-carmine). *a*, Branched and dilated glandular spaces cut longitudinally; *b*, same, cut transversely; *c*, stroma. × 27.

the other. Through the formation of papillary excrescences on the inner walls of the gland-spaces there is formed an *adenoma papilliferum*.

The *stroma* supporting the glands consists in part of preëxisting connective tissue, and in part of that which has been newly formed.

Adenomata develop either in normal tissue, malformed tissue, in tissues which have been altered by disease (inflamed mucous membrane, cirrhotic

FIG. 320.—Adenoma mammæ alveolare (alcohol, alum-carmine). *a*, Terminal alveoli; *b*, gland-ducts; *c*, connective-tissue stroma. × 27.

liver, contracted kidney, ovaries containing scar tissue), or from *remains of fœtal structures.* The new-formation of glands is dependent upon a pro-

liferation of the surface-epithelium or of glandular epithelium, the steps or this process being similar to those occurring in the regeneration of normal gland-tissue. The beginning of the adenomatous proliferation may be recognized by changes in the form and staining of the cells. This is particularly easy in the case of the stomach and intestine in which adenomatous proliferations so often develop in connection with inflammatory and ulcerative processes. The change of the gland-cells into high cylindrical cells staining intensely may occur at the same time or successively in a number of glands and is then followed by cell-proliferation and new-formation of glands.

The cause of the new-formation of gland-tissue within normal organs is wholly unknown. Glandular new-formations developing in tissues which have been altered by inflammation, and which lead to tumor-like growths, may in the beginning bear the character of a regenerative or hyperplastic new formation, and for this reason the *adenomata cannot be sharply differentiated from regenerative and hyperplastic proliferations.*

Fig. 321.—Developing papillary adenoma of the kidney. (Alcohol, hæmatoxylin, picrofuchsin.) *a*, *b*. Fully developed tumor-tissue; *c*, *d*, early stages of development of the tumor. × 150.

Tubular adenomata represent the most common form of the adenomata. They occur particularly in mucous membranes (Figs. 317; 318, *f*) provided with tubular glands (intestine, uterus); but are found also in such glands as the breast (Fig. 319), liver, ovary, and not infrequently in the kidneys. They are characterized by the formation of simple and branched gland-tubules (Figs. 317, *a*, *b*; 318, *f*; and 319, *a*, *b*) which are lined by simple columnar or cubical epithelium and form nodular tumors varying in size from that of a pea to that of an apple or a man's fist, or rarely even larger.

The **alveolar adenomata** arise from glands (mamma, ovary, thyroid, sebaceous glands); and are characterized by the formation of numerous terminal berry-like alveoli (Fig. 320, *a*), as well as gland-ducts (*b*).

Papillary adenomata (Fig. 321, *a*) arise through the formation within the tubules of an adenoma, of little elevations of epithelium into each of which a connective-tissue papilla grows. The local epithelial proliferation (*c*) and the formation of papillæ (*d*) may accompany the atypical gland-formation.

The **stroma of an adenoma** is at times well developed, at other times but slightly, and consequently adenomata may be divided into *hard* (mammary gland) and *soft varieties* (kidney, liver, ovary, testicle). An especially marked development of the connective tissue leads to the for-

mation of **fibro-adenomata** or *fibrous adenomata*. Such forms occur most frequently in the mammary gland.

If, as happens not infrequently in the mammary gland, the connective-tissue proliferation in an adenoma is not of a diffuse character, but takes place particularly around the canaliculi (see Fig. 250), the tumor is ordinarily designated as a *fibroma pericanaliculare*. If, as the result of more marked local proliferative activity on the part of the connective tissue (Fig. 322, *c*, *d*, *e*), an ingrowth of rather broad and short papillæ

FIG. 322.—Fibroma intracanaliculare mammæ (fibro-adenoma papilliferum) (alcohol, alum-carmine). *a*, Dense, intercanalicular growth of fibrous tissue; *b*, pericanalicular tissue rich in cells; *c*, *d*, *e*, nodular, intracanalicular connective-tissue proliferations cut longitudinally; *f*, intracanalicular proliferations cut transversely. × [illegible].

(*e*) into the gland-spaces takes place, the resulting tumor is known as a **fibroma intracanaliculare.** According to its genesis such a tumor may also be appropriately designated a **fibro-adenoma papilliferum.**

Adenomata cannot be sharply differentiated from tumor-like glandular hypertrophies on the one hand, and carcinomata on the other. For example, in the healing of intestinal ulcers the regenerative processes in the glands may be so active as to give rise to polypoid formations, which may either be called *glandular hypertrophies* of the mucous membrane, or *adenomata*, according to the individual standpoint. Likewise, different names may be applied to the glandular polypi which occur so frequently in the uterus.

The *carcinomatous nature* of a new-growth resembling an adenoma (see § 121) is generally made evident by a more marked epithelial proliferation and by its infiltrative mode of growth There are, however, adenomata, having a single layer of columnar cells, which grow by infiltration (particularly in the intestine), and thereby assume the character of malignant tumors. They should accordingly be classed with the carcino-

mata, and must be designated as *adenocarcinoma*. On the other hand, there are also adenomata with marked atypical epithelial proliferation (mamma, endometrium), which —for a long time at least—do not show any malignant characteristics.

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§ 120. A **cystadenoma** or **adenocystoma** is an *adenoma whose gland-spaces have undergone cystic dilatation through the accumulation of secretions.* Such tumors are usually composed of numerous cysts, and are, therefore, designated as **multilocular cystomata.** According to the character of the cyst-wall there may be distinguished a *smooth-walled* or *simple cystoma* (*cystoma simplex*), or a *papilliferous cystoma* (*cystoma papilliferum*).

FIG. 323.- Section of a cystadenoma ovarii papilliferum (Müller's fluid, hæmatoxylin). × 40.

Small amounts of secretion are often seen in the ordinary adenomata (Fig. 317), and the spaces of both simple and papillary adenomata are often so wide (Figs. 319, *a*; 322) that they at once attract the eye on cross-section of the growth. In cystadenomata such cyst-formation is the predominating feature.

The early stages of the cysts are represented by *gland-tubules* of varying shape (Figs. 323 and 324, *b*), which lie in a more or less richly developed connective-tissue stroma. Through the accumulation of secre-

tion these tubules become gradually dilated so that numerous small cysts arise (Fig. 325), or else both large and small cysts (Figs. 326–330) are

FIG. 324.—Adenocystoma of the bile-passages in the first stages of development (alcohol, hæmatoxylin). *a*, Liver tissue; *b*, adenoma tissue in the periportal connective tissue. × 90.

formed. Often the relationship is such that the tumor may consist of a few large cysts (Fig. 329) in whose walls smaller cysts occur; or there

FIG. 325. FIG. 326.

FIG. 325.—Section of a portion of a multilocular adenocystoma of the ovary. Reduced about one-sixth.

FIG. 326.—Section through an adenocystoma of the testis of a four-year-old boy. Natural size.

FIG. 327. Multilocular adenocystoma of the liver, seen in section. *a*, Liver parenchyma; *b*, membranous margin of the left lobe; *c*, *d*, large cysts; *e*, group of smaller cysts, separated from each other only by connective tissue; *f*, portal vein; *g*, hepatic artery. Two-thirds natural size.

FIG. 328.—Cystoma of the kidney, cut transversely. Eleven-fourteenths natural size.

may be found, by the side of large cysts (Fig. 327, *c*), portions of tissue, which contain only small cysts (*e*) or even appear solid—that is, consisting of a tissue the glands of which are not dilated.

FIG. 329.—Adenocystoma ovarii partim simplex, partim papilliferum. *a*, Smooth-walled cysts; *b*, soft papillary growth covered with simple, mucus-forming cylindrical epithelium. (Metastatic nodules were present in the peritoneum.) Reduced one-third.

All the different varieties of cystomata may develop in the ovaries (Figs. 325 and 329), testicles (Fig. 326), liver (Figs. 324 and 327), kidneys (Fig. 328), and the mammary glands.

FIG. 330.—Portion of a papillary adenocystoma of the ovary, seen in section. (Drawn from a specimen hardened in chromic acid.) Four-fifths natural size.

In the ovaries cystomata not infrequently develop coincidently on both sides, and may be associated with dermoid formations. Adenocystomata of the testicles not infrequently inclose within their stroma foci of cartilage or other tissue, so that such growths should be classed with the *teratomata* (§ 128).

The *epithelial lining* of cystomata is usually composed of simple columnar cells, but may be a ciliated, cubical, or flattened epithelium.

The cyst-contents usually consist of a clear, often distinctly ropy fluid, which contains a mucin-like substance (pseudomucin, see § 59). This substance is a product of the epithelial lining in which goblet-cells are often found (Fig. 331, *c*). Not infrequently the fluid also contains whitish flakes, the products of cells which have undergone fatty degeneration; or it may be more or less cloudy or reddish or brownish from previously occurring hæmorrhages. An abundant secretion in many cysts may lead to the formation of tumors of enormous size; in the ovary, for example, they may reach a weight of from ten to twelve kilograms or more.

The **papillary adenocystomata** constitute a common variety of adenocystoma. They are characterized by the fact that sooner or later papillary excrescences develop in the glands which have undergone cystic degeneration.

In the adenocystomata of the ovary these excrescences are usually slender and delicate, forming villous-like outgrowths (Fig. 330) or cauli-

FIG. 331.—Cystoma papilliferum ovarii (Müller's fluid, hæmatoxylin, eosin). *a*, Stroma with papillæ; *b*, gland-tubule with small papillæ; *c*, high cylindrical epithelium; *d*, mucus-containing cells, within the cyst-spaces. × 150.

flower elevations, which may fill up a larger or smaller part of the cysts. Minute papillary elevations, extending over an extensive area of the inner surface of the cyst-wall, may give to the latter a velvety appear-

ance similar to that of a mucous membrane. If the excrescences develop in cysts of small size, they may fill these, and the tissue may thereby take on the appearance of a dense, non-cystic, medullary tumor, though from the cut surface more or less mucus can usually be obtained.

Larger papillæ are always more or less branched (Fig. 331), and consist of a cellular stroma (*a*), whose surface is usually covered with tall

FIG. 332.—Papillary adenocystoma of the ovary with myxomatous degeneration of the connective tissue of the papillæ (Müller's fluid, hæmatoxylin). *a*, Fibrous stroma; *b*, papillæ which have undergone myxomatous change; *c*, epithelium. × 80.

columnar cells (*c*) of the character of goblet-cells. The contents of the cysts consist of ropy mucus (*d*) mingled with more or less numerous desquamated cells which have undergone mucous degeneration, or the remains of such cells. In rare cases the connective tissue of the papillæ may undergo a mucous degeneration (Fig. 332, *a*, *b*), and may swell to a marked degree, and finally become changed into myxomatous spheres covered externally with epithelium.

Adenocystomata of the liver, testicles, and kidneys usually form no papillæ, or at most very small ones. In the papillary adenocystomata of the mammary gland the excrescences are usually broad and plump (Fig. 333), as is the case with those of the papillary adenomata (Fig. 322). Accordingly, on the cross-section of such tumors the cyst-spaces are found to be filled with polypoid proliferations of various forms (Fig. 333), which are often flattened through mutual pressure, and give to the surface of such a cross-section a laminated appearance.

Since in these tumors the connective-tissue elements predominate over the epithelial, these growths are often classed with the *connective-tissue tumors*, and designated, according to the character of the connective tissue, as *cystofibroma*, *cystomyxoma*, or *cystosarcoma*. When showing a structure of leaf-like layers they have received the name of *sarcoma phyllodes*.

The *papillary adenocystomata* show a *certain malignancy*, even when the papillæ are covered with a simple epithelium (see cystocarcinoma).

This is shown in the first place, in the fact that the papillary proliferations may break through the cyst-wall, in the case of such tumors of both the ovary and mammary gland, and in the latter situation they may

FIG. 333.—Papillary cystoma or intracanalicular papillary fibroma of the breast, laid open by a longitudinal incision. One-half natural size.

also break through the skin. Papillary ovarian cystomata (Fig. 329, *b*) may in this way give rise to metastases in the peritoneal cavity, and these in turn display the characteristics of papillary epitheliomata.

The *adenocystomata* represent a variety of tumor which possesses no sharply defined limits; for example, papillary cystomata may arise from the development of papillary excrescences in dilatation-cysts which are formed from pre-existing glands (see § 118). Further, malformations of organs—for example, of the kidneys (Fig. 328)—may lead to the formation of multilocular cystomata, the cystic dilatation affecting not only the urinary tubules, but also *Müller's* capsules. That teratomata may appear in the form of adenocystomata has already been mentioned in the text. Finally, a transition from cystadenoma to cystocarcinoma may also take place.

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See also § 119.

(c) *Carcinoma and Cystocarcinoma.*

§ 121. The **carcinomata** are *malignant epithelial tumors* characterized by *infiltrative growth* and the *formation* of *metastases*.

They develop:

(1) In the skin, mucous membranes and in glands, all of which appeared to be normal, before the development of the carcinoma.

(2) In the skin, mucous membranes, and in glands, which have already suffered changes before the development of the carcinoma.

(3) In already existing papillary epitheliomata, adenomata and adenocystomata.

(4) From the remains of fœtal epithelial structures, and from epithelial tissues which have been misplaced through disturbances of development, and have already developed into pathological formations.

(5) From the epithelial tissues of the chorionic villi and placenta.

The most essential characteristic of the development of a carcinoma is that presented by **atypical proliferations of epithelium which sooner or later penetrate into the tissue bordering upon the affected glands or surface-epithelium.** This phenomenon is usually accompanied by a **proliferation of connective tissue**; but this is not absolutely essential

to the development of a carcinoma. The tissue invaded by the epithelial proliferation—whether glandular tissue, muscle, bone, etc.—is sooner or later destroyed by the growth, although within the stroma of the carcinoma there may occur a new-formation of other tissue than connective tissue, as, for example, bone.

The **cause of the atypical growth of epithelium** is not known with certainty; it can only be said that certain conditions favor such growth. Thus, for example, *old age* predisposes to the development of carcinomata of the skin, inasmuch as in this period of life the connective tissue of the skin undergoes a certain amount of atrophy and becomes looser in structure, while the epithelium, at least in part, continues to increase, and under certain conditions shows here and there distinct evidences of increased activity (formation of coarser hairs upon the nasal septum, lobes of the ears, and in the eyebrows). Likewise carcinomata of the mucous membranes and the glands usually appear in the later years of life, although they may occur earlier in life, even in childhood.

A further *predisposition to the development* of carcinoma is found in *regenerative processes* following the destruction of surface epithelium and glandular tissue. These occur most frequently in *old inflammatory processes* that have led to tissue-destruction and new-formations of tissue, particularly in the mucous membrane of the intestinal tract, gall-bladder, and uterus, and also in glands and in the skin. In the stomach the round ulcer (*Ulcus ex digestione*) may form the starting-point of a cancer. In the first place the regenerative proliferation following the tissue-injury may form the basis for an atypical malignant proliferation. In addition an important rôle is played by the *snaring-off and misplacement of epithelial cells into the neighboring altered connective tissue*, a phenomenon of frequent occurrence in the healing of ulcers, the growth of epithelium over granulation-tissue, and in tuberculosis, and other chronic infective granulomata, both in the mucous membranes and skin and also in glands.

All these predisposing factors do not constitute the unique cause of the development of a carcinoma. They may exist for a long time without giving rise to a cancer. It appears that something else must be added to cause the unlimited atypical proliferation of epithelium, and what this something is is at present unknown. Whether this cause is to be found in a bioplastic stimulus comparable to that of fertilization or in chemical influences stimulating the cells to increased proliferation or in the removal of the influences that inhibit and regulate proliferation cannot be stated at the present time.

In recent years the opinion has been many times advanced and maintained that **parasites** cause carcinomatous and sarcomatous proliferations. But the majority of the appearances which have been described as parasites (as protozoa, especially sporozoa, and as yeast-fungi) have not been parasites at all, but degenerated nuclei and nuclear division-figures, or leucocytes inclosed within tumor-cells, or degeneration-products of such, or products of cell-protoplasm, particularly keratohyalin and colloid, or epithelial hyalin and mucin. In the few cases in which true parasites were present in the tissues, this occurrence could very well have been a secondary infection, which in no way could be regarded as a cause of the development of the tumor. *In not a single case has it been proved beyond all doubt that parasites have been the cause of either carcinoma or sarcoma.*

Certain portions of the intestinal tract—the rectum, the flexures of the colon, the pylorus and cardia of the stomach, the œsophagus

pharynx, tongue, and gums—are favorite seats for the development of cancer. Cancer may develop in any portion of the skin, but it occurs more frequently on the lips and nose than on the remaining portions of the face, or on the extremities, and on these again more frequently than on the trunk. Of the sexual apparatus the parts most commonly affected are the mammary gland and cervical portion of the uterus; less frequently, though relatively often, the ovary, testicles, body of the uterus, vulva, vagina, and penis. The liver, kidneys, bladder, trachea, bronchi, lungs and pancreas occupy a middle ground; while the larynx and gall-bladder are, on the other hand, more frequently affected.

Cancer usually develops in the form of *nodules, which are not sharply differentiated* from the neighboring tissues; on the mucous membranes they are not infrequently elevated above the surface in the form of *sponge-like*, or *polypoid*, or *papillary growths.* From the point of origin they spread by an **infiltrative growth** of the epithelial proliferations, by which either the nodules increase in size or there are formed diffuse superficial thickenings, as in the case of the intestinal wall. The ovaries, testicles, uterus, kidneys, etc., may be partly or wholly transformed into carcinomatous tissue. Often the boundaries of the organ originally affected are overstepped, and the epithelial infiltration extends into neighboring tissues and organs. Thus, for example, a carcinoma of the mamma may infiltrate the neighboring fat, skin, and muscle; one of the gums, the maxillary bone; one of the uterus, the vagina, parametrium, bladder, and rectum; a cancer of the gall-bladder may involve the liver; one of the thyroid, the trachea; and one arising in the bronchi, the lungs, etc.

The **formation** of **metastases** may take place either through the lymph- or blood-vessels, and is of very frequent occurrence by both routes. It leads to the development of secondary nodules in different organs; but it may happen that large lymphatic areas—as, for example, the lymphatics of the lung—may be simply dilated by the new-growth, without the formation of circumscribed nodules. The transportation of cancer-cells to the bone-marrow may lead to a carcinomatous degeneration of the marrow of an entire bone or of several associated bones. Moreover, it should be noted that probably not every transportation of cancer-cells is followed by the development of a cancer, but that many of the cells so transplanted die.

The **tissue of a carcinoma** is sometimes white and soft like marrow, sometimes firm and dense; but it is almost always possible to obtain from the cut surface more or less of a whitish, cloudy fluid called *cancer juice* or *cancer milk.* Very often the cut surface presents a tough, fibrous framework in the meshes of which the softer masses lie; and from which the latter may be squeezed out by pressure either in the form of fluid, or as plugs or as crumbling masses.

The masses obtained from the cut surface through pressure and scraping consist, for the chief part, of **atypically proliferating epithelial cells,** the so-called **cancer-cells,** which are found in a *great variety of forms,* and usually show degenerative changes, particularly fatty degeneration. A true *secretion* of these epithelial cells is usually not found; but cancers occur—particularly in the mucous membranes, ovaries, mammary glands, and thyroid—which produce mucin, pseudomucin, or colloid. The amount of secretion may at times be so abundant as to lead to the formation of cysts and thereby to *cystocarcinoma.*

Retrograde changes occur very often in cancers at an early stage.

They are caused partly by the feeble vitality of the new growth, partly by circulatory disturbances, which may be due to the filling-up of capillaries and veins by the ingrowing cancer-cells, and partly by external causes. These changes lead, in the first place, to a ***destruction of cancer-cells*** in certain portions of the tumor and the formation of central cavities due to the liquefaction of the dead portions, so that, after resorption of the dead material, the tissues often sink in, and in this way depressions are caused over the surface of the tumor-nodules. Such depressed areas are seen particularly upon primary cancer-nodules in the mammary gland, and on secondary nodules in the liver, lungs, and other internal organs, and are often spoken of as ***cancer-umbilications.***

The retrograde changes often lead to complete destruction of tumor-tissue, and thereby to the **formation of ulcers.** This occurs particularly in cancers of the mucous membranes, these growths at the patient's death usually revealing a more or less extensive ulceration; but such ulcerations also take place in carcinomata of the mammary glands and skin. In the latter situation the cancer may take on the appearance of a rodent ulcer. The edge of such ulcers is sometimes elevated and resembles a wall, or it may be studded with nodules; at other times it is more sharply defined and only slightly infiltrated. The base of the ulcer is sometimes fissured and ragged, and covered with necrotic tissue; at other times it is smooth.

The view that the **cause of carcinoma and sarcoma is to be found in parasites** still finds adherents, although the investigations of recent years do not support it. Publications concerning cancer and sarcoma parasites have not been wanting (*Sanfelice, Roncali, Aievoli, Maffuci, Secchi, Foà, Ruffer, Plimmer, Gaylord, Wlaeff, Sjöbring, Schüller, von Leyden, Feinberg, Leopold, Podwyssotzki*, and others), but in the majority of cases proof has been wanting that the supposed parasites were really living organisms; or, when living organisms (yeasts, rhizopods) have been cultivated from tumors, there has been no positive proof that they stood in any causal relation to the given neoplasm. The experiments, in particular, of *Sanfelice, Wlaeff, Leopold*, and *Sjöbring* are far from offering any convincing evidence.

It is very striking and worthy of note that nearly every author has found a different parasite and has not recognized the parasitic forms described by the others. This speaks against the correct interpretation of the findings. Moreover, in the case of the majority of the formations described as parasites another interpretation is possible. Some of them are degenerating leucocytes or the remains of such enclosed in cancer-cells; others are vacuoles, hyaline or mucoid products of the cancer-cells, or degenerating nuclei or cell-division figures, or fragments of these. Only rarely is it impossible to give a satisfactory interpretation of the findings, but this fact is not sufficient grounds for ascribing a parasitic nature to the formations. The attempt to compare the "bird's eyes" of von Leyden, or the Plimmer's bodies, to which they correspond, with the parasite found in the root-tumors of cabbage, the *Plasmodiophora brassicæ*, and to regard these root-tumors as analogous to cancer, is, likewise, without justification, since the two diseases have scarcely anything in common. The plasmodiophora multiplies within the plant-cells and distends the latter. Only after the destruction of the affected cells does a regenerative proliferation occur in the neighboring cells. In cancer there is from the very beginning an unlimited and at the same time an infiltrative growth of tissue-cells.

The natural history and clinical behavior of cancer are not such as to make it probable that it is of parasitic nature. The formation of cancerous tumors as a result of disturbances of development speaks against this view. The metastases develop from transported tumor-cells, and cell-inclusions are not necessary to their formation. The transplantation of cancer and sarcoma into animals of the same species, and the implantation-cancers occasionally observed after operation, are the result wholly of the transplantation of living tumor-cells, and cannot be used as arguments in favor of the parasitic theory. If protozoa are the cause of cancer we must assume, according to our present knowledge of these parasites, that a given species can find a suitable soil only in a certain variety of epithelium. Cases of transmission of cancer from man to man occasionally cited as evidence can be utilized hypothetically in support of the

parasitic theory only when the cancer develops in the affected individual in the same mother-tissue.

To increase our knowledge concerning the cause of cancer a committee was appointed to study the statistics, and through a collective investigation on October 15th, 1900, attempted to determine the number of living cancer-patients in Germany. In so far as the view of the parasitic nature of cancer is concerned this work was negative, since in only 3.6 per cent (of 12,179 cases) was an infection suspected. A hereditary transmission was thought possible in 17 per cent, but the number was reduced to 4.3 per cent when the possibility of such an inheritance was limited to those cases in which the same organ was affected. Since 1888 the number of cancer-cases is said to have increased about a third, but even this statistical evidence is without significance since it may be satisfactorily explained as the result of greater skill in diagnosis as well as the result of an increase in the average length of life. Moreover, it should be noted that even now many cases of cancer (cancer of stomach) are not diagnosed even up to death, and on the other hand cases are regarded as cancer when occurring in tissues in which carcinoma does not develop. (The statistics mentioned above contain 201 cases of primary carcinomata of the bones.)

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See also § 122.

§ 122. The **development of carcinoma of the skin** takes place most often from the *surface epithelium*, and is characterized essentially by the growth of the interpapillary portions of the same into the deeper portions of the skin, in the form of epithelial plugs (Fig. 334, *d*) which fill up the connective-tissue spaces. The stratum corneum (*c*) may also undergo hypertrophy along with the cells of the rete Malpighii, and penetrate into the deeper tissues with the epithelial plugs (*d*). Moreover, the horny cells which get into the deeper tissues may form epithelial pearls (*e*).

Besides the surface-epithelium, the *epithelium of the hair-follicles* and *sebaceous glands* may also take part in the development of the cancer: and there occur carcinomata of the skin, which develop entirely from

the sebaceous glands, and therefore should be classed with the gland-cancers.

The *connective tissue* may remain entirely passive during the ingrowth of the epithelium, but is sooner or later excited to growth (Fig. 334, *a*), and the papillæ often develop into long, branched formations (*f*). In

b

a

FIG. 334.—Transverse section through a carcinoma of the lip (alcohol, hæmatoxylin, eosin). *a*, Corium, in a state of proliferation; *b*, epithelium; *c*, thickened horny layer; *d*, epithelial plugs extending into the corium; *e*, epithelial plugs with horny pearls, cut obliquely; *f*, enlarged papillæ. × 12.

the proliferating connective tissue there are often found in association with the *fibroblasts* also *leucocytes* and *lymphocytes*, which may penetrate into the epithelium. They become especially numerous in the event of tissue-destruction, so that under such circumstances the proliferation of the connective tissue acquires wholly the character of an inflammatory granulation-tissue.

The **origin of the carcinomata arising from mucous membranes covered with squamous epithelium** may be the same as that of a cancer of the skin—that is, it is introduced by a *proliferation of the surface epithelium* (Fig. 335, *a*, *c*). If *glands* are present they may also *take part in the development of the cancer*. It is a remarkable fact that in the formation of such a tumor, glands with cylindrical epithelium may furnish epithelial products which correspond with those of the surface-epithelium. The epithelial proliferation may at first be intracanalicular and lead to a diffuse thickening and stratification of the epithelium (Fig. 335, *f*), or to the formation of excrescences (*e*). Later, the proliferating epithelium breaks into the connective tissue.

The connective tissue behaves in the same manner as in the case of cancer of the skin.

The **cylindrical-celled carcinomata of the mucous membranes** arise in the case of the intestine from the *tubular glands* or from the *crypts*, the epithelium of which at first undergoes an active proliferation, and becomes stratified, while the glands become dilated (Fig. 336, *b*). Later, the glands become changed into branching, atypically formed structures (*c*), which possess an epithelium arranged in many layers, and which grow into the neighboring tissues.

In the stomach the gastric glands change their character (Fig. 337, *f*), and then through a continued growth infiltrate the submucosa (*g*), the muscularis (*d*), and the serosa (*e*).

The epithelium of the newly-formed glands stains more deeply with nuclear stains than does normal epithelium.

The connective tissue, as in the case of *cancer* of the skin, sooner or later proliferates, and in connection with this proliferation there may occur also an emigration of leucocytes and lymphocytes.

The **development of cancer in glands**—as, for example, in the mammary gland—likewise begins with an *epithelial proliferation*, as the result of which the glands (Fig. 338, *a*) become widened, altered in form, *b* while their lining epithelium becomes stratified (*b*). With the breaking through of the epithelium into the neighboring connective-tissue spaces, the epithelial infiltration of that tissue is begun. According to the structure of the gland in which the cancer arises, and according to the

FIG. 338.—Beginning development of carcinoma in the vaginal portion of the uterus (alcohol, Bismarck-brown). *a*, Epithelium; *b*, connective tissue; *c*, surface epithelium growing into the deeper tissue; *d*, dilated glands; *e*, glandular epithelium growing out in form of plugs; *f*, cross-section of a gland, the cylindrical epithelium of which has become converted into stratified epithelium. × 45.

variety of the cancer itself, there will be produced varying microscopical pictures.

The *connective tissue* of the gland through proliferation also takes part in the building-up of the tumor; but in the early stages of development such proliferation may be slight or entirely wanting.

The **development of a carcinoma in an adenoma** or fibro-adenoma

(Fig. 339, *a*) is likewise initiated by a change in the character of the cells and by a *more active proliferation of the epithelium*, through which the simple epithelium becomes stratified (*b*, *c*). The later ingrowth of the

FIG. 338.—Developing adenocarcinoma of the large intestine (Müller's fluid, hæmatoxylin, eosin). *a*, Mucosa with unchanged glands; *b*, glands showing carcinomatous change; *c*, carcinomatous areas in the submucosa. × 100.

epithelium into the connective tissue, which often occurs at a very late stage, is a further sign of malignancy—that is, of the carcinomatous transformation of the new-growth.

FIG. 339.—Adenocarcinoma of stomach in process of development (formalin, alcohol, hæmatoxylin, eosin). *a*, Mucosa; *b*, muscularis mucosæ; *c*, submucosa; *d*, muscularis; *e*, serosa; *f*, *g*, adenocarcinoma. × 15.

The **development of carcinoma from papillary epitheliomata** takes place in the same manner as from the normal skin and mucous mem-

branes; and is characterized especially by the infiltration of the epithelium into the basement-tissue upon which the epithelioma rests.

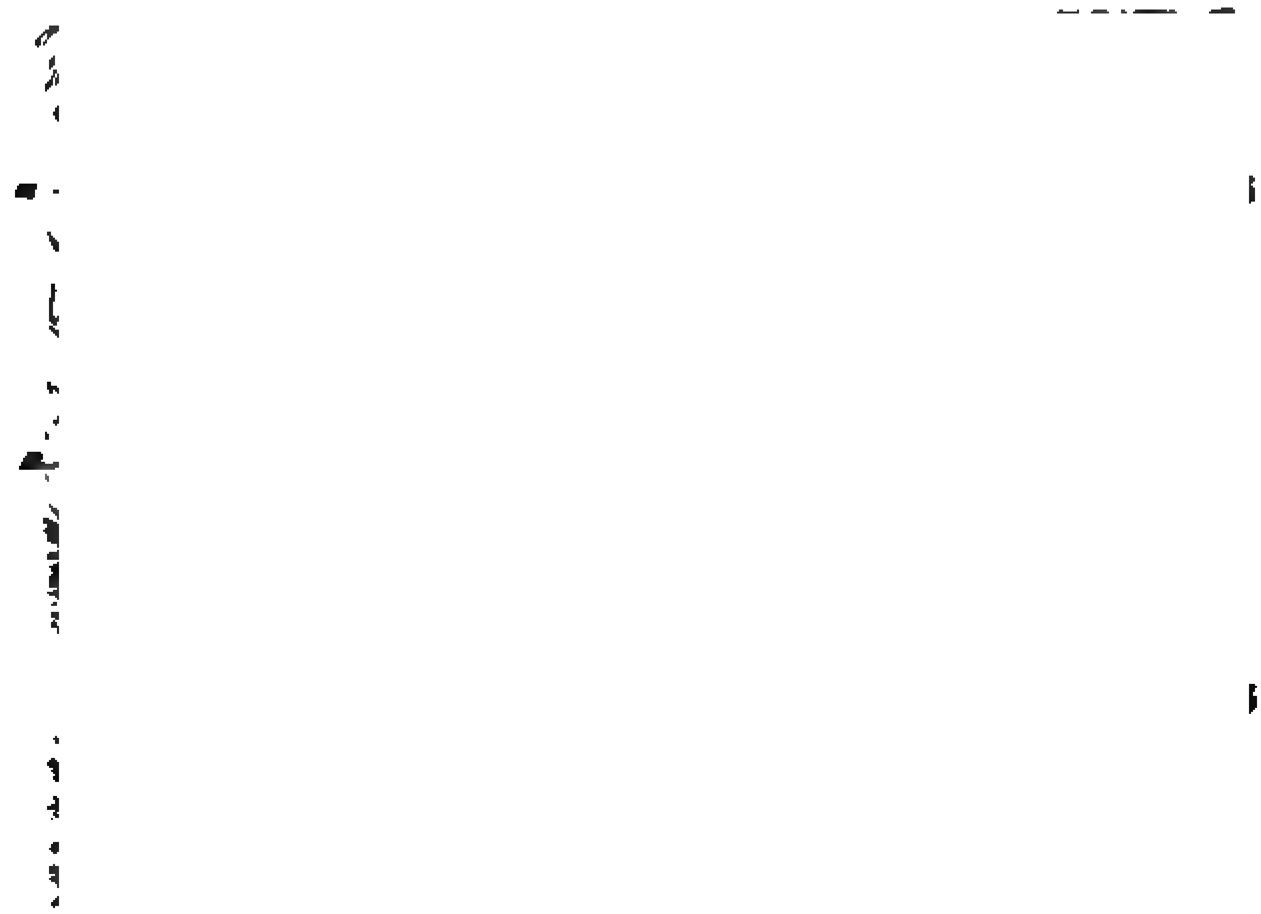

FIG. [illegible].—Developing cystocarcinoma of mamma (alcohol, hæmatoxylin). Tumor of the size of a bean. *a*, Normal gland-tissue; *b*, proliferating gland-tissue. × [illegible].

FIG. [illegible].—Tubular adenoma of mamma showing a beginning transition to carcinoma (formalin, hæmatoxylin). *a*, Branching gland-tubules with simple epithelium; the periacinous connective tissue is proliferating and very cellular; *b*, *c*, gland-tubules, the epithelium of which is partly simple, partly stratified. × [illegible].

The **development of carcinoma from transplanted or misplaced epithelium or from remains of fœtal structures** proceeds in the same manner as that of carcinomata arising in either surface or glandular epithelium.

Carcinomatous proliferations of the cell-layer and the syncytium of the chorion, both of which arise from the **fœtal ectoderm** (Bonnet), may occur either in the chorion of young ova or in the placenta of older embryos, and in atypical cases are characterized by a mixture of the two forms of cells (Fig. 340, *a*, *b*). They grow into the neighboring uterine

FIG. 340.—Intravascular epithelial plug of a placental carcinoma. (Formalin, alcohol, hæmatoxylin, eosin.) *a*, Derivatives of the cell-layer; *b*, syncytial cells; *c*, wall of blood-vessel; *d*, blood. × 40.

tissue, particularly into the blood-vessels of the uterus (*c*), and may through the formation of thrombi lead to extensive destruction of the tissues of the uterus, and may give rise to metastases. Myxomatous degeneration of the chorion or placental villi (hydatid mole) appears to favor the development of such carcinomatous growths.

The **development and growth of carcinoma** have been in recent years the object of searching investigations. Besides *Ribbert* and *Borst*, who have expressed their views in their works on tumors, *Krompecher*, *Hauser*, *Petersen* and *Colmers*, and *Borrmann* have published treatises of considerable size upon these questions. All of these writers agree that the developing neoplasm, in so far as its epithelial elements are concerned, grows through its own resources and does not excite the neighboring tissue, that is, neighboring epithelium, to a cancerous proliferation. The neighboring tissue is in part compressed and in part infiltrated. On the other hand, differences of opinion exist concerning the beginning of the cancerous growth. According to *Hauser*, *Krompecher*, *Petersen* and *Colmers*, the development may be unicentric or multicentric, in the latter case starting in several places in the epithelium. *Borrmann* assumes a unicentric

origin; in those cases in which the development apparently proceeds from several places he assumes that there is a coincidental development of several primary cancers.

According to *Hauser*, *Krompecher*, and *Petersen*, with whom I agree, the development of carcinoma takes place from cells of the superficial epithelium, hair-follicles, glands, and gland-ducts. According to *Borrmann*, a developing carcinoma is a growing cell-complex, which existed as such before it began to grow; it is an isolated embryonal cell-complex. Squamous-celled cancers, although not all of them, arise from extremely small cell-complexes that lie within the superficial epithelium, and probably become isolated during fœtal life through a closure of a furrow or through some other anomaly of development.

According to the first-named authors, the pathological new-formation has its origin from epithelium or at least takes its point of departure from it. According to *Borrmann* and *Ribbert*, the process begins with inflammatory changes in the connective tissue; in the skin these may be caused by a retention and infection of the secretion of the sebaceous glands causing an elevation and stretching of the epithelium. As the result of this stretching and the accompanying hyperæmia, the included fœtal cell-complex proliferates and grows into the deeper tissues.

The independent proliferations of the fœtal ectoderm are at this time usually designated as **chorioepithelioma** (*Marchand*) in accordance with the view that they represent an epithelial proliferation. There is no reason for not classing them with the **carcinomata,** since they are characterized by an epithelial proliferation which infiltrates the neighboring tissues. The metastasis through the blood-vessels which characterizes the chorionic carcinomata occurs also very frequently in other carcinomata, for example, carcinomata of the stomach.

Carcinomata arising in the skin or mucous membranes are often called **cancroids,** a term used to distinguish them from other carcinomata, the origin of which was formerly thought to be from connective tissue.

To a certain extent the character of the parent tissue is preserved in cancer-cells, but a careful examination shows in all cases that there is a certain amount of change both in their morphological and in their physiological character (*anaplasia*). This is shown in changes in the form and structure of the cells, their changed behavior toward stains, in an altered position and arrangement of the cells, and in their changed relations toward the surrounding tissues.

The traumatic displacement of surface-epithelium in wounds may lead to the formation of the so-called **traumatic epithelial cysts**—that is, cysts varying in size from that of a hemp-seed to that of a nut, which are lined with epithelium, and, in case they arise from the epidermis, contain a pultaceous mass of desquamated epithelium. They occur most frequently after puncture-wounds of the volar surface of the fingers and in the hollow of the hand.

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§ 123. The **structure of a carcinoma** is determined by its origin. The manner in which the epithelium proliferates and the associated pro-

FIG. 341.—Horny cancer of the tongue (Müller's fluid, hæmatoxylin, eosin). *a*, Epithelial plugs with epithelial pearls; *b*, stroma. × 100.

liferation of the connective tissue make it possible to distinguish a **connective-tissue stroma** which contains the blood-vessels, and **nests** and **strands of cells**—the so-called **cancer-plugs**—which lie embedded in the stroma. If the cancer grows into a tissue having a special structure, the stroma may contain muscle-fibres, bone trabeculæ, unchanged glandular tissue, etc.; but these tissues usually die after a time. In general a carcinoma possesses an **alveolar structure**, at times suggesting an imperfectly developed acinous gland, at other times a tubular gland, so that it is possible to distinguish *acinous* and *tubular* types of carcinoma. When the cell-plugs are solid, without a lumen, the growth may be called a **carcinoma solidum** or merely **carcinoma.** The presence of a lumen in the cell-plugs gives to the growth an appearance resembling anatomically the adenomata, and warrants the designation **carcinoma adenomatosum** or **adenocarcinoma.**

FIG. 342.—Carcinoma of the skin, with delicate cellular network and areas of hyaline connective tissue. (Alcohol, hæmatoxylin.) × 80.

The **type of carcinoma** is to a certain degree *dependent upon the parent-tissue* in which it arises, and the cells may still show the characteristics

of the parent epithelium. Squamous-celled carcinoma may be expected to occur wherever there is squamous-celled epithelium, and cylindrical-celled carcinomata in mucous membranes having cylindrical cells. Cornification takes place in carcinomata of the skin, mucoid degeneration in those of mucous membranes, while the formation of colloid occurs in those arising from the thyroid. Departures from this rule are, however, common, in that the epithelial cells may remain at a less highly differentiated stage, so that the type of the cell-variety concerned may not be developed to its fullest; or it may happen that the cells lose their

FIG. 342.—Adenocarcinoma recti tubulare (alcohol, alum-carmine). *a*, *b*, Epithelial gland-tubules; *c*, c_1, stroma; *d*, collections of leucocytes in the gland-tubules. × 65.

original character and take on others. For example, colloid-like substances may be formed in cancers of the skin, mucus may be produced in mammary cancers, or horny squamous-celled carcinomata may develop in mucous membranes possessing cylindrical epithelium (gall-bladder) or in those having transitional epithelium (pelvis of kidney).

(1) **Squamous-celled cancers** develop in the **skin** and in those **mucous membranes covered with squamous cells.** They occur, therefore, in the external skin, mouth cavity, pharynx, œsophagus, larynx, vaginal portion of the cervix, vagina, and external genitals. In rare cases they may develop in mucous membranes possessing cylindrical epithelium—for example, in the trachea and gall-bladder—or in the remains of fœtal structures—for example, in the remains of the branchial clefts, and in dermoids.

The flat-celled cancer is characterized chiefly by the formation of relatively large cell-nests (Figs. 341, *a*) of irregular shape; but they often form also small strands of cells. The epithelial cells which are collected in masses show clearly the character of stratified squamous epithelium with the formation of prickle-cells, but on account of their multiplication within the tissue-spaces are usually *polymorphous*, and no longer manifest their typical characteristics. Very often the formation of keratohyalin and cornification takes place within the large epithelial plugs which have penetrated into the deeper tissues. The cells which have undergone a horny change become arranged in concentric laminæ

resembling those of an onion (Fig. 341, *o*). Such cell-nests are known as *epithelial pearls* or *horny bodies*, and give occasion for the designation of the tumor as a *horny cancer*. If, instead of cornification, the central

FIG. 344.—Adenocarcinoma fundi uteri. *a*, Stroma; *b*, cancer-plugs; *c*, isolated cancer-cells. × 150.

FIG. 345.—Carcinoma simplex mammæ (alcohol, hæmatoxylin). *a*, Stroma; *b*, cancer-plugs; *c*, isolated cancer-cells; *d*, blood-vessels; *e*, small-celled infiltration of the stroma. × 200.

portions of the cell-nests undergo necrosis and liquefaction, the carcinoma may take on an *adenoma-like* structure.

Besides these typical flat-celled cancers there often occur in the skin and mucous membranes possessing squamous cells **carcinomata having**

FIG. 346.—Acinous carcinoma of the mammary gland with large nests of cells (Müller's fluid, hæmatoxylin). × 100.

epithelium persisting at a lower stage of development, so that the cell-strands remain slender and delicate, and consist of small epithelial cells of different forms (Fig. 342) that do not change into prickle-cells

FIG. 347.—Tubular scirrhous cancer of the mammary gland (Müller's fluid, hæmatoxylin). *a*, Area with well-developed elongated nests of cells; *b*, portion of tumor in which the cell-nests have for the greater part disappeared. × 100.

and horny cells. Krompecher designates such cancers as *basal-celled carcinomata,* since they develop from the layer of basal cells. The cell-cords of these carcinomata are usually solid, but through the production

of hyaline cell-products in the centre of the cell-masses they may take on an *adenomatous* appearance.

(2) **Cylindrical-celled carcinomata** develop chiefly in those mucous membranes possessing cylindrical epithelium—intestines, stomach, respiratory tract, body of the uterus, and gall-bladder, but occur also in glands—ovary, mammary gland, liver, etc.—as well as in the cerebral ventricles. Such tumors exhibit, at least in the early stages of development, the character of **carcinoma adenomatosum** or **adenocarcinoma** (Figs. 336, 337, 343), and also form epithelial structures which resemble glands and consist of variously formed gland tubules lined by a simple or stratified epithelium. A more active proliferation of the epithelial cells leads finally to the formation of compact cell-nests possessing no lumen (Fig. 344).

The stroma of cylindrical-celled carcinomata is usually poorly developed; and the tumor consequently bears the character of a soft cancer, a **carcinoma medullare.** Nevertheless the cancerous tissue may in some cases possess a firm consistence.

(3) The **carcinoma simplex** or *carcinoma in the narrower sense*—that is, a cancer whose especial characteristics are derived from the form and position of the cancer-cells, in that these are arranged simply in irregular, compact heaps (carcinoma solidum)—occurs most frequently in glands, but may develop also in the mucous membranes and skin. The cell-nests are in part very irregularly shaped (Fig. 345), in part round (Fig. 346), or in other cases elongated or fusiform (Fig. 347). These variations have given occasion to the employment of the terms **carcinoma acinosum** (Fig. 346) and **carcinoma tubulare** (Fig. 347) as distinguishing types of corresponding character. It should be noted, however,

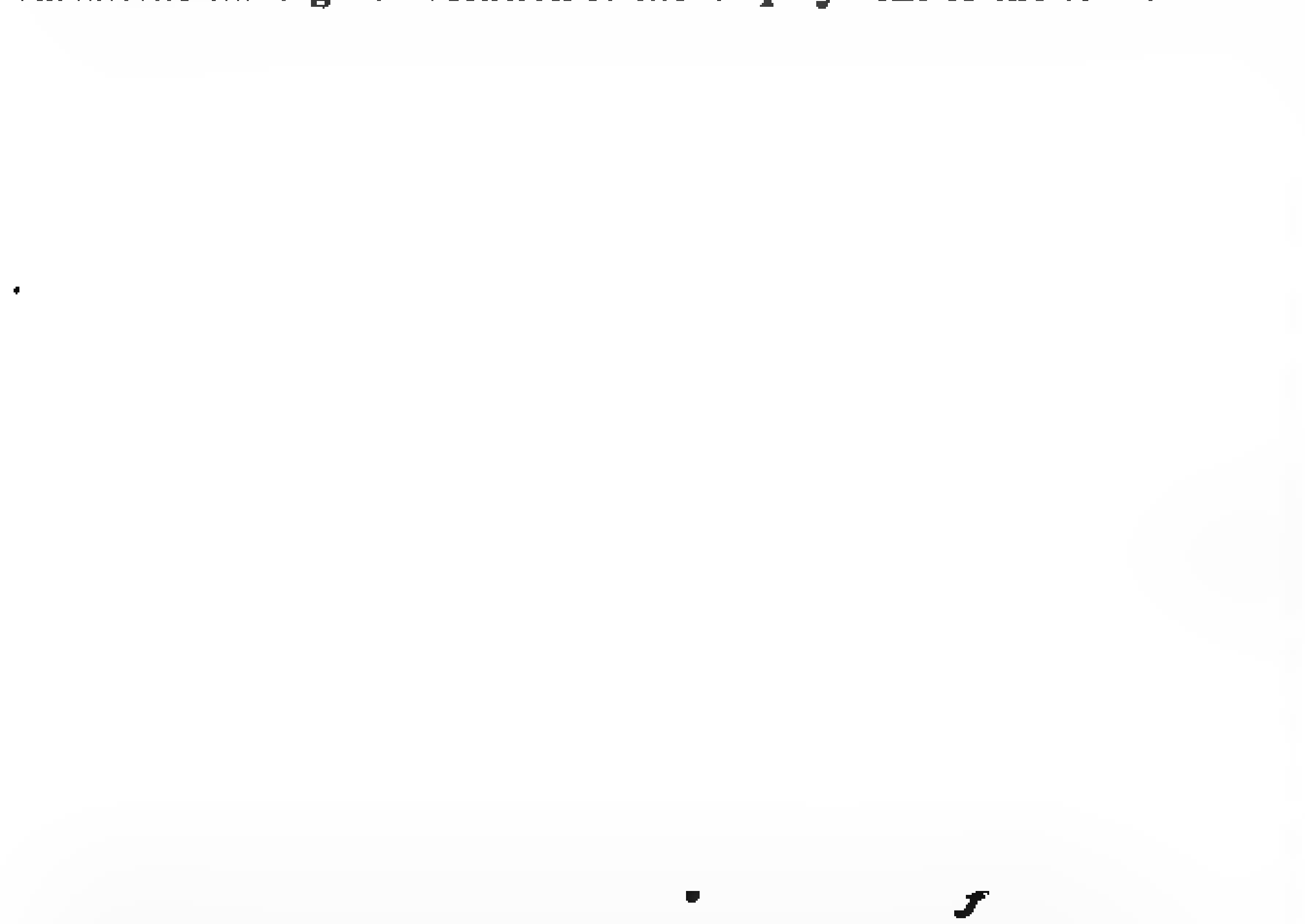

FIG. 348.—Section through a segment of a carcinoma of the breast (alcohol, hæmatoxylin). *a*, Nipple; *b*, tissue of gland; *c*, skin; *d*, gland-ducts; *e*, carcinomatous masses occupying the place of the gland tissue; *f*, carcinomatous infiltration of fat tissue; *g*, portion of skin infiltrated with carcinoma; *h*, nests of cancer-cells in the nipple; *i*, normal gland-lobule; *k*, small-celled infiltration of the connective tissue. Magnified by hand-lens.

that these different types may be present in the same tumor (Fig. 348, *e*, *f*, *g*), since the character of the cell-nests depends partly upon their manner of growth and partly upon that of the connective-tissue stroma in which they develop. At the seat of origin of the tumor the cell-nests may have a variety of shapes (*e*); in adipose tissue they are rounded (*f*); in the unyielding connective tissue of the skin they are small and fusiform (*g*).

An abundant development of cell-nests within a delicate connective-tissue stroma leads to the formation of a **carcinoma medullare.** A marked development of the connective-tissue stroma with the formation of relatively few cancer-cells gives rise to a hard tumor, which is called a **carcinoma durum** or a **scirrhus** (Fig. 347).

FIG. 349.—Mucoid carcinoma of the mammary gland (Müller's fluid, hæmatoxylin, eosin). *a*, Normal gland tissue; *b*, *c*, early stages of carcinomatous proliferation with beginning formation of mucus; *d*, larger cell-nests with masses of mucus; *e*, *f*, carcinoma tissue showing marked mucous degeneration. × 30.

The hard variety of cancer owes its origin to the fact that the cell-nests are from the beginning relatively few and small, while the connective-tissue stroma is abundant and hard. Such tumors are formed especially when the epithelial proliferation infiltrates into hard connective tissue, as, for example, in the mammary gland and skin, but the same characteristics may be exhibited in the case of newly-formed connective tissue. In the course of time a cancer becomes harder by reason of the destruction of a large portion or of all of the nests of epithelial cells (Fig. 347, *b*), while the connective tissue increases in amount. An originally **soft cancer may become hard** through a more or less pronounced **shrinkage of the cancerous tissue** in association with the **induration of**

a

b
c

d

e

FIG. 350.—Early stages of development of a mucoid carcinoma of stomach, arising in an atrophic mucosa (formalin, alcohol, hæmatoxylin, eosin). *a*, mucosa; *b*, muscularis mucosæ; *c*, submucosa; *d*, muscularis; *e*, serosa; *f*, *g*, Mucoid cancer. × 9.

the tissue. Carcinomata of the mammary gland, stomach, and intestine very often show such secondary hardening, and in cancer which has undergone such a fibrous change the nests of cancer-cells may be entirely absent.

(4) The **chorion-carcinoma** or **malignant chorio-epithelioma** is distinguished from other carcinomata by the presence in the individual cell-masses of a mixture of various cell-forms (Fig. 340, *a*, *b*) belonging to the fœtal ectoderm. Such a combination is not everywhere present, and does not occur especially where single cells or cell-groups penetrate into the blood-stream or are transported passively. The conditions favoring a development within the blood-vessels are found when fluid and coagulated masses of blood lie between the tumor-cells (*c*).

FIG. 351.—Carcinoma mucosum mammæ (alcohol, hæmatoxylin). *a*, Stroma; *b*, cancer-plugs; *c*, alveoli without cancer-cells; *d*, cells containing spherules of mucus. × 200.

(5) **Cancers characterized by peculiar secondary changes** arise through the formation of especial products by the cancer cells, or through peculiar metamorphoses of the same, or more rarely through changes in the stroma.

Mucoid or gelatinous cancer—carcinoma mucosum (*C. gelatinosum*, *C. colloides*)—is that form of carcinoma in which the epithelial cells produce mucus (mucin or pseudomucin) or a more colloid-like gelatinous substance. Such production of mucus occurs particularly in cancers of

the intestine, stomach (Fig. 350), and mammary gland (Fig. 349); and may be manifest in the earliest stages of the development of the tumor (Figs. 349, *b*, *c*; 350, *f*, *g*), so that the mucoid products of the cells collect first in the centre of the cell-nests after the manner of a gland-secretion. Later the border of cells surrounding the mucoid material is broken through, the cells pushed aside, separated from the underlying structures, and crowded toward the centre of the mucus-containing alveolus (Fig. 349, *d*, *e*, *f*). Ultimately, the epithelial cells are wholly destroyed.

FIG. 352.—Carcinoma with hyaline drops within the cell-nests (Carcinoma cylindromatosum). *a*, Cell-nest without; *b*, cell-nest with a few hyaline spherules; *c*, cells which have been reduced to strands arranged in a network, as the result of the formation of numerous hyaline spherules. × 150.

In intestinal cancers the formation of mucin takes place in goblet-cells, which are similar to the goblet-cells occurring under normal conditions. In cancer of the breast the mucus appears in the form of droplets within the cancer-cells (Fig. 351, *d*), and becomes free either by escaping from the cell, or through the complete destruction of the cell itself.

Through the development of mucoid or colloid-like masses within the cancer-cell nests, the latter may become studded with hyaline drops, and thereby acquire a mesh-like appearance (Fig. 352). Such formations were formerly designated as *cylindromata*, and classified with the corresponding sarcomata. Should it be thought desirable to retain this nomenclature, such a tumor may be designated *carcinoma cylindromatosum*; but it seems unnecessary to separate these growths from the mucoid and colloid carcinomata.

FIG. 353.—Enlarged hydropic cancer-cells, from a carcinoma of the mamma (Müller's fluid, Bismarck-brown). *a*, Ordinary cancer-cells; *b*, hydropic cells containing drops of fluid; *c*, swollen nucleus; *d*, swollen nucleolus; *e*, wandering cells. × 300.

When the cancer-cells attain an extraordinarily large size, as occurs, for example, in flat-celled cancers or in cancers of the breast, the tumor may be termed a **carcinoma gigantocellulare.** If the enlargement of the cells is not due to an increase in the amount of protoplasm, but to a swollen condition of the cells or to a collection of drops of fluid in the cells and their nuclei (Fig. 353), the cells are designated *physalides* (*carcinoma physaliferum*).

Myxomatous degeneration of the connective-tissue stroma may occur in portions of a cancer, so that the cancer-cells become separated from each other by myxomatous tissue (Fig. 354, *c*). Such growths may be called *carcinoma myxomatosum.*

Hyaline degeneration of the connective tissue occurs in different forms of cancer, but is usually confined to small areas of the tumor.

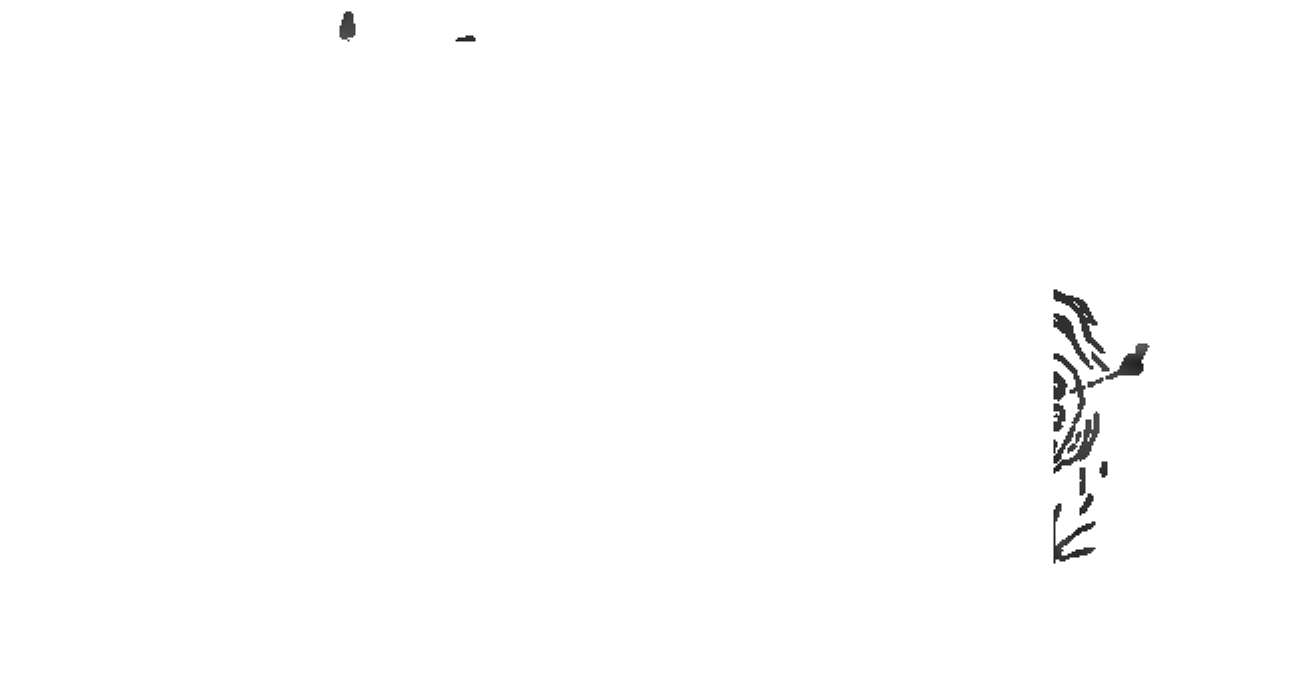

FIG. 354.—Carcinoma myxomatodes ventriculi (Müller's fluid, hæmatoxylin). *a*, Cancer-plug; *b*, connective-tissue stroma; *c*, stroma of myxomatous tissue; *d*, cancer-cells which have undergone serous degeneration. × 200.

Deposits of lime-salts in carcinomata occur chiefly as concretion-like masses, similar to those found in psammomata. The concretions may form either from the cells or in the connective tissue. They are observed particularly in papillary adenomata and carcinomata of the ovary, and in cancers of the mammary gland. There also occur more extensive calcifications, which may lead to complete **petrifaction**; and tumors showing such changes occur chiefly in the skin and subcutaneous tissues, in

FIG. 355.—Adenosarcoma malignum of the kidney, from a child seven years of age (formalin, hæmatoxylin, eosin). *a*, Tissue with gland-tubules; *b*, sarcoma-like tissue. × 300.

the form of sharply defined, hard, rounded nodules. Some of these

tumors, according to the descriptions given, are to be classed with the carcinomata, others represent calcified atheromata or adenomata of the sebaceous glands.

If, at the same time with development of the epithelial new-growth, there occurs a marked proliferation of the connective tissue, leading to the formation of a very cellular tissue, there arise tumors which, according to their structure, may be designated **adenosarcoma** or **sarcocarcinoma.** Typical examples of this form of tumor occur in the kidneys (Fig. 355, *a*, *b*), forming medullary tumors, the origin of which is probably to be referred to a disturbance of development of the kidney. Such tumors may show a varying structure in different parts, at one time more of an adenomatous or carcinomatous character, at another time only a sarcomatous. The metastases of such tumors exhibit a similar character.

Spontaneous healing of carcinomata does not take place, but many of them grow very slowly, and many processes within cancers may be interpreted as *local attempts at healing*. In this category belong especially the degenerative processes in the cancer-cells that lead to their death and dissolution, so that finally in large areas of the neoplasm (for example, in cancer of the stomach) there may be found only hyperplastic masses of connective tissue, but no more cancer-cells. It is very probable that in the destruction of the cells proteolytic ferments may play a rôle. The occurrence of calcification in a cancer depends upon a previous death of its cells. Further, the fact that transported cancer-cells (compare § 125) do not always give rise to daughter-tumors, but very frequently die at the place where they lodge, may be interpreted as a healing process.

Various authors (*Becher*, *Petersen*, *Schwarz*, *Orth*) would also look upon the occurrence of giant-cells within tumors as a process of healing; it would be more correct, however, to say that in the course of certain retrograde processes giant-cells may appear. The cause of the retrogression lies not in the giant-cells; they appear only under certain conditions, and especially when in cancers corpuscular elements of certain kinds, cornified cells in particular, come in contact with connective tissue. They are nothing more than foreign-body giant-cells, and their occurrence is to be regarded only as secondary to certain retrograde processes.

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See also §§ 122 and 124.

§ 124. The **cystocarcinomata** represent a form of tumor which stands in the same relation to cancer as the cystadenomata do to the adenomata. The majority of cancers form no demonstrable secretion, but there occur certain varieties, particularly in the group of adenocarcinomata, in which the epithelial cells produce mucus or colloid (thyroid), and in adenocarcinomata of the liver a secretion of bile has been observed (Schmidt). In cystocarcinomata the mucous secretion of the epithelium may lead to the formation of large spaces filled with fluid. Cystocarcinomata occur chiefly in the ovary and mammary gland, usually bearing the character of a **cystocarcinoma papilliferum** (Fig. 356), in that the cyst-spaces, in certain parts or throughout, are either partially (*b*, *c*) or wholly (*d*, *e*) filled with papillary proliferations. These excrescences

FIG. 356. Cystocarcinoma papilliferum mammæ. *a*, Stroma; *b*, smooth-walled cysts; *c*, cysts containing papillary proliferations; *d*, cysts entirely filled with papillary proliferations; *e*, small cysts with papillary growths; *f*, adenomatous proliferations; *g*, papilla of the mamma. Reduced about one-third.

possess a soft, medullary appearance, and when developed in great numbers give to the entire tumor a marrow-like character.

Both the cyst-wall and the papillary proliferations, which branch in the same manner as do those of the papillary cystadenomata, are covered with a thick, stratified layer of epithelium (Fig. 357, *b*, *c*, *d*; 358, *c*).

The papillæ are usually slender (Fig. 357, *c*, *d*), but through *myxomatous degeneration* of their connective tissue may attain a large size (Fig. 358,

FIG. 357.—Cystocarcinoma papilliferum ovarii (Müller's fluid, hæmatoxylin). *a*, Stroma; *b*, epithelium; *c*, *d*, papillæ. × 72.

b). Through total *myxomatous degeneration of the connective tissue* of the papillæ the latter may ultimately become converted into *mucous cysts* surrounded by epithelium. If at the same time the epithelial layers of

FIG. 358.—Papillary cystocarcinoma of the mamma with papillæ which have undergone myxomatous degeneration (Müller's fluid, hæmatoxylin, eosin). *a*, Dense connective tissue; *b*, myxomatous papillæ; *c*, proliferating epithelium, arranged in several layers. × 78.

neighboring papillæ become confluent, the epithelium finally comes to represent a stroma which incloses balls of mucus.

The metastases of cystocarcinomata may have the character of cauliflower-like, papillary growths, and this is particularly the case when ovarian tumors of this nature spread throughout the peritoneal cavity. Other metastases show the characteristics of ordinary carcinomata.

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See also § 122.

§ 125. **Growth by infiltration and the involvement of the surrounding tissues** takes place, during the early stages of development (Sec. 122), through the penetration of the epithelial elements alone into the neighboring tissue in the form of connected plugs or cords of cells. Not infrequently there appear in the tissue-spaces single epithelial cells that

FIG. [illegible]. Colloid-containing cancer of thyroid infiltrating the thyroid cartilage [illegible]. a, Cartilage; b, cancer-tissue; c, colloid; d, cancer-tissue growing into the cartilage.

multiply and form strands or round masses of cells. In the growth of a tumor into neighboring organs, the connective-tissue stroma (Fig. 379, d) surrounding the cell-nests breaks into the neighboring tissue (a) and replaces it. Such a mode of infiltration occurs to the most marked degree in the case of carcinomatous infiltration of cartilage (a) and bones.

The **formation of metastases**, which takes place more frequently in

the case of carcinoma than any other form of tumor, is the natural result of its infiltrative mode of growth. In the process of infiltration the *cancer-cells break into the lymph-vessels* (Fig. 244), and through these are carried to the lymph-glands. In both places there results a multiplication of the transported cancer-cells (Figs. 244, *a*; 360, *d*). In the lymph-glands the lymphadenoid tissue becomes replaced by cancer tissue; the lymphocytes vanish, while the connective tissue of the lymph-gland serves as a framework for the cancer.

The development of cancer in the lymph-channels is either limited to the filling and distention of the lymph-vessels by the cancer-cells (Fig. 244) or it may likewise lead to the formation in this situation of daughter-nodules.

The epithelial obstruction of the lymph-vessels is often very extensive; and through the blocking-up of individual lymph-channels or of the thoracic duct itself, a *retrograde metastasis of cancer-cells may be caused.* For example, in the case of a cancer of the stomach the lymph-vessels of the mesentery and the thoracic duct, and those of the lungs, or even of the upper extremities, may become the seat of metastatic growths. Through the thoracic duct cancer-cells may be carried into the blood-stream.

The *epithelial proliferation breaks into blood-vessels* not less frequently than into the lymphatics; and the invasion of the veins by cancer-cells is to be regarded as a constant phenomenon. In consequence the vessel-lumen becomes filled with cancer-cells, and at a later stage the affected portion of the vessel becomes converted into cancer-tissue, the framework of which is formed through the proliferation of the constituents of the more or less altered vessel-wall.

FIG. 360.—Section from an enlarged axillary gland, with beginning development of cancer (alcohol, hæmatoxylin). *a*, Germ-centre of a lymph-node; *b*, lymph-sinuses; *c*, artery; *d*, nests of cancer-cells. × 60.

If cancer-cells pass from the thoracic duct or from a vein into the circulation there are formed *hæmatogenous metastases.* In carcinoma of

the stomach and intestine cancer-cells are very often carried through the portal vein into the liver (Fig. 245, *b*, *c*). The thoracic duct and the systemic veins permit a transportation of cancer-cells to the lungs. According to investigations by M. B. Schmidt, the lungs are very frequently the seat of metastases, but in many cases these do not develop into nodules visible macroscopically. Much more frequently only microscopic intra-arterial groups of cancer-cells embedded in thrombi are found. A part of these metastases can through the proliferation of the tumor-cells develop into daughter-nodules, and the lungs may contain numbers of these. Very often, however, the transported cells fail to develop into cancer-nodules (Schmidt). The transported cells, that perhaps have re-

FIG. 361. FIG. 362.

FIG. 361.—Metastatic collection of young cancer-cells within a liver-capillary, arising from a primary adenocarcinoma of the stomach (alcohol, hæmatoxylin). × 300.

FIG. 362.—Metastatic development of cancer within the liver-capillaries, arising from a primary carcinoma of the pancreas (alcohol, carmine). Both connective tissue and nests of carcinoma cells have developed within the capillaries. × 250.

cently proliferated, die, and there occurs only a proliferation of connective tissue in the vessel-wall, leading to the organization of the thrombus. In other cases the cancer-cells increase within the vessel-lumen without forming large nodules.

When *cancer-cells enter the systemic circulation* there occurs a *distribution of the carcinoma to the various organs.* It is not yet known to what extent the transported cells die. The favorite seats of secondary development of cancer are the bones, liver, and kidneys. Occasionally a development of carcinoma may take place in all the organs of the body, so that the resulting condition may be styled a *general carcinomatosis.*

The *secondary cancer-foci* develop first intravascularly (Figs. 361, 362, and 363, *c*). In the beginning the neighboring tissues are but little changed (Fig. 363). Later there occur in part tissue-degenerations (Fig. 363, *f*) and in part connective-tissue proliferations (Figs. 362, 364, *c*, *d*), and the newly formed connective tissue serves as the stroma for the developing cancer-nodule. The amount of this connective tissue varies greatly, and is dependent in part upon the parent-tissue in which the tumor develops and in part upon the variety of cancer. The most

a

c

b

a

FIG. 363.—Carcinomatous metastases in the upper layer of the uterine mucosa, in universal carcinomatosis following carcinoma of the mamma. (Formalin, hæmatoxylin and eosin.) *a*, Muscularis of the uterus; *b*, normal mucosa; *c*, nests of cancer-cells in the vessels between the uterine glands; *d*, upper layer of the mucosa densely infiltrated with nests of cancer-cells; *e*, uterine epithelium; *f*, ulcerated area. (Blood-clots containing cancer-cells were found in the uterus.) × 100.

b

a

c

d

FIG. 364.—Metastatic development of cancer in the diploë of the skull-cap in primary carcinoma of the stomach. (Formalin, hæmatoxylin, eosin.) *a*, Marrow-tissue; *b*, nest of cancer-cells; *c*, proliferated endosteum with nests of cancer-cells; *d*, fully developed area of carcinoma. × 40.

marked connective-tissue proliferation occurs in the cancer-metastases in bones (Fig. 364), particularly when there is a diffuse growth of the carcinoma through the bone. With the destruction of the old bone the carcinoma may form in place of the bone-substance an abundant fibrous stroma in which osteoid tissue or new bone may be formed in large amounts. It would appear that many carcinomata must produce substances that excite a marked proliferation of the periosteum and endosteum. Similar marked proliferations may occasionally be observed when carcinomata spread over the serous membranes, particularly the periosteum.

As has already been mentioned in § 101, **carcinomata may be transplanted to individuals of the same** species, and after operations **implantation-carcinomata** may develop.

Recurrences after the removal of the tumor by operation are very common in the case of cancers, and in advanced cases can scarcely be avoided. They arise usually from remains of the primary tumor or from metastases already present in the body either in the immediate neighborhood or in distant organs. In rare cases the conditions favoring the growth of the cancer may again arise in the neighborhood of the scar resulting from the operation, so that after several years a *new cancer* develops.

Recurrences and **metastases of the chorionic carcinomata** grow extremely rapidly so that within a few days tumors of considerable size may be formed. The dark-red color shows even to the naked eye that blood is largely concerned in their make-up, and the microscopical examination shows that the rapid increase in size is in a large measure due to the large hemorrhages caused by the development of the tumor. The epithelial masses may form a relatively small part of the entire bulk of the growth.

Chorion carcinomata, that is, the epithelial cell-masses characteristic of these tumors, have been repeatedly observed *ouside of the uterus*, in various organs (*Schmauch, Schmorl, Risel, Busse, Zagorjanski-Kissel*), also in *cardiac thrombi* (*Busse*), *without any tumor of the uterus having been demonstrable.* This phenomenon may be explained by the fact that the epithelial cells of the normal chorion or of the hydatid mole, that is, of myxomatous chorionic villi, may be transported through the blood-stream and proliferate without the development of a tumor at the placental site.

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See also § 101.

3. The Teratoid Tumors and Cysts.

§ 126. Under the head of **teratoid tumors and cysts** may be grouped those tumor-like formations which are characterized by the fact that the tissue-formations of which they are composed either do not occur normally at the site in question (*heterotopous growth*), or at least do not normally appear there at the time at which they are found (*heterochronous growth*). Part of the teratoid tumors and cysts, which are classed as **teratomata** in the narrower sense, exhibit, moreover, the peculiarity that they are *composed of a variety of tissues.*

The teratoid tumors and cysts may be conveniently divided, according to their structure and their origin, into three groups, as follows: (1) *The simple teratoid tumors;* (2) *the simple teratoid cysts;* (3) *the complex teratomata, which in part contain tissues derived from all the germ-layers.*

The **heterotopous tissue-growths**, which are classed with the teratoid tumors may occur in the most various organs, but are more frequently found in certain regions than in others. Among the more common tumors of this class are the chondromata and chondromyxomata of the salivary glands and the testicle, osteomata of the muscles, lipomata of the pia mater, adenosarcomata of the kidney containing striped muscle, and the adrenal tumors found in the kidney. Among those occurring more rarely are the chondromata and osteomata of the skin or of the mammary gland, rhabdomyomata of the testicle, etc.

The occurrence of tissue-formations in regions in which such tissues are not normally present can be explained in part by the assumption that **cells** or **groups of cells** of a tissue have not undergone a normal differentiation into definite tissue-forms, but **retain the capacity of forming different kinds of tissues.** Nevertheless, in many cases the explanation is to be sought rather in a **germinal aberration** or a **misplacement of tissue,** in that either in early embryonic life embryonal cells of one organ find their way into the anlage of another organ, or that, later, tissues in process of development or already formed are displaced from their normal position. The first process can be inferred only from the subsequent appearance of pathological tissue-formations; the latter, on the other hand, may at times be recognized, later on, in the anatomical relations. Thus, for example, in the retrograde changes occurring in hernias of the sacral portion of the spinal cord, adipose tissue and muscle-tissue may find their way into the spinal canal and the arachnoidal sac and grow around the nerves. Arnold observed transposition of fat-tissue, gland-tissue, cartilage, and neuroglia at the lower end of the trunk, in a case of myelocyst with complete absence of the lumbar, sacral, and coccygeal portions of the spinal column. He also found in a lipomatous teratoma of the frontal region that the intracranial portion of the tumor communicated with the extracranial through a defect in the cranium.

The **teratoid cysts** may be divided into two great groups: the *ectodermal* on the one hand, and the *entodermal* and *mesodermal epithelial cysts* on the other.

The **ectodermal cysts** vary in size from that of a pea to that of a man's fist. Their walls present ectodermal characteristics, either in that they consist only of a smooth connective-tissue membrane, covered with stratified squamous cells—the so-called **epidermoids**; or the cyst walls may present all the characteristics of skin—that is, contain papillæ, sebaceous glands, hair follicles, hairs and sweat-glands, and often also subcutaneous fat—the so-called **dermoids** or **dermoid cysts** or **dermatocysts.**

The cyst-contents consist either of desquamated horny cells alone, or of such cells, fat, and blond hair.

Epidermoids and *dermoids* are found chiefly in the *skin* and *subcutaneous tissues*, where they present themselves in the form of *tumors containing a pultaceous material*, which resemble *atheromata*, i.e., tumors caused by the retention of secretion in the excretory ducts of the sebaceous glands and in the hair-follicles. They are also found at the sides of the *neck* and in the median line either above or below the hyoid bone; further, in the *thoracic cavity*, particularly in the *mediastinum*, in the *peritoneal cavity* (rarely), *pelvic cellular tissue, coccygeal region*, and in the *raphé of the perineum*. Finally, they also appear *within the cranium*, in the dura or in the hypophysis. Of frequent occurrence are the intracranial formations which are known as **cholesteatoma** or as **pearl tumors.** These growths vary in size from that of a pea to that of an apple; they form spherical or nodular tumors, having a white satiny surface, and consist for the chief part of thin, non-nucleated, scale-like cells, arranged in closely crowded laminæ. They are invariably situated at some point on the pia (Boström), and at such places the vascular pia is covered with stratified squamous cells, which in the course of years produce the delicate epithelial scales of which the tumor is composed. The neighboring brain tissue and the arachnoid, which may in part extend over the growth, are not concerned in the formation of the horny scales. In rare cases cholesteatomata may contain *sebaceous material* and *fine hairs* in addition to the horny scales and cholesterin. In these cases there may be found seated here and there upon the pia *dermal structures*, i.e., true skin tissue containing *sebaceous glands* and *hair-follicles*, from which the sebaceous material and hairs found in the growth arise. The simple cholesteatomata may therefore be designated as **epidermoids** (Boström), those containing hair as **dermoids.** Cholesteatomata occur at the base of the brain, in the neighborhood of the olfactory lobe, tuber cinereum, corpus callosum, choroid plexus, pons, medulla oblongata (very rarely in the spinal cord), and in the cerebellum.

The dermoids and epidermoids under consideration probably owe their origin to a **transplantation of epithelial germs to the sites** in question. In the case of the epidermoids probably only embryonal epithelial cells are transplanted; in dermoids embryonal dermal tissue is also transplanted. The intracranial cholesteatomata originate probably in an early implantation of epidermal anlage in the pia. Mediastinal dermoids probably depend upon disturbances of development of the thymus, which arises from the ectoderm. The dermoids on the sides of the neck arise from remains of the branchial clefts, particularly of the second; those hanging from the hyoid bone or lying beneath it are probably to be regarded as the remains of the ductus thyreoglossus. Dermoids of the pelvic cellular tissue may be explained as arising from epithelial inshoots from the perineum.

Simple **entodermal** and **mesodermal epithelial cysts** are characterized by a lining of cylindrical cells, which are often *ciliated.* They occur most frequently in the broad ligament and tubes. They are found also in other portions of the peritoneal cavity, in the intestine, in the neighborhood of the trachea and bronchi, in the lungs, pleura, neck, tongue, vagina, glandular organs, etc. They form cysts varying in size from that of a pin-head to that of a man's head.

The occurrence of these cysts may be explained in most cases by the

persistence of fœtal glands or canals or by the **separation through constriction of portions of entodermal or mesodermal epithelial tubes.** In the neck remains of the internal branchial clefts, in the posterior portions of the tongue the remains of the ductus thyreoglossus or of epithelial buds and glands developing from the same, in the œsophagus and respiratory tract snared-off portions of the intestinal canal or of the air-passages, or remains of the communication between alimentary tract and air-passages, may form the foundation for the development of such cysts. In the broad ligament, uterus wall, and tubes the cysts arise from remains of the canals of the Wolffian duct and the duct of Gärtner; in the tubes, cervix, portio vaginalis, vagina, and hymen they

Fig. 365.—Adenoma-like isolation in the submucosa of a portion of the mucous membrane of the small intestine, giving rise to a ridge-like prominence of the mucosa 2 cm. in length (alcohol, hæmatoxylin). From a child six weeks of age. *a*, *b*, *c*, Normal intestinal wall; *d*, *e*, portions of mucosa included within the submucosa; *f*, mucous tissue rich in cells. × 85.

arise from the remains of the latter; in the peritoneal cavity in part from snared-off portions of the intestine (*enterocysts*), or in part from portions of the urachus (*urachus-cysts*). Within the glands—for example, the liver or the kidneys—portions of the gland-tubules may become constricted off during the period of development, and later develop into cysts (*adenocysts*).

Cysts located in the central nervous system or its immediate neighborhood—for example, at the lower end of the trunk—may arise from the medullary canal (*myelocysts*), in the latter place also from remains of the hind-gut (*enterocysts*).

The origin of the cysts lined with cylindrical epithelium can usually be determined only from their position and the character of their walls, but in the majority of cases the origin can usually be ascertained beyond doubt. The diagnosis can be made with the greatest certainty when the misplacement of the separated portion is slight (Fig. 365, *d*, *e*), and when the formation still shows clearly the character of the mother-tissue.

The significance of ectodermal, entodermal, and mesodermal cysts is dependent upon their position, size, and the secondary changes which occur in them. Their size varies from that of a pin-head to that of a man's head. Among the *secondary changes*—aside from *inflammation*—may be mentioned the development of *adenomata* and *carcinomata*. For example, remains of the Wolffian body which are present in the dorsal wall of the uterus near the angles of the tubes (von Recklinghausen), or

FIG. 366.—Adenoma-like remains of the Wolffian body, within the uterine musculature (formalin, alcohol, hæmatoxylin, eosin). *a*, Muscle tissue; *b*, glandular tissue; *c*, sections of vessels. × 100.

in the broad ligament in the inguinal region (Aschoff, Pick) may give rise to adenomata, cystadenomata (Fig. 366, *b*), or adenomyomata. *Dermoids* may be the seat of development of a *squamous-celled cancer* (branchiogenic and subcutaneous carcinoma); while from separated portions of the intestinal mucous membrane (Fig. 365) it is probable that cylindrical-celled carcinomata may take their origin. *Cysts, cystadenomata*, and *carcinomata* may develop in the jaw from misplaced portions of the *epithelial anlage of the teeth.*

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See also § 128.

§ 127. **Complex teratomata** occur most frequently in the sexual glands, partly in the form of *dermoid cysts* and partly as *solid tumors associated with multiple cyst-formation.* The first occur particularly in the ovary, the latter in the testicles.

The so-called **dermoid cysts** of the ovary form rather thick-walled cysts, varying in size from that of a pea to that of a man's head, and are filled with a fatty material containing blond hair. At some point in the wall there will be found extending into the cyst-cavity a *villus-like, nodular, flattened,* or *septum-like prominence, which is covered with hairs and*

FIG. 367.—Portion of the wall of a dermoid cyst of the ovary. *a*, Smooth wall; *b*, prominence consisting of fat and cutaneous tissues; *c*, swollen protuberance, bent down upon itself above and bearing hairs and teeth (*d*). Natural size.

often studded with teeth (Fig. 367, *b*, *c*, *d*). The upper layers of this prominence contain the characteristic structures of the skin (Fig. 368,

a, a_1, a_2, b), namely, hair-follicles with hairs, sebaceous glands, and sweat-glands; subcutaneous fat is also usually present (f). In the deeper layers are found other tissue-formations, such as cysts and tubes lined with ciliated columnar epithelium (d), bone (g), cartilage, teeth (h),

FIG. 368.—Section through a prominence in a multilocular dermoid (alcohol, nitric acid, hæmatoxylin, eosin). a, a_1, a_2, Epidermis; b, corium with sebaceous glands; c, sinus lined with squamous epithelium; d, sinus lined with cylindrical epithelium; e, tubular glands; f, fat-tissue; g, bone; h, teeth; i, brain-tissue with corpora amylacea; k, ovarian tissue. × 5.

muscle-tissue (also heart-muscle [Katsurada]), brain-tissue (i), nerves, groups of ganglion-cells, mucous glands, intestinal mucosa, and thyroid tissue, as well as pigmented formations resembling the rudimentary tissues of the eye. Kidney and liver tissues have not yet been found. The remaining portion of the cyst-wall of the dermoid is either covered with cylindrical epithelium or is bare; if hairs are present in this portion, they are the result of a secondary implantation, and may be surrounded by granulation-tissue, often also by giant-cells. If in association with the cysts containing fat and hairs there are also found cysts filled with a serous or mucoid fluid, the latter may be explained as arising through the cystic dilatation of spaces of the dermoid which are lined with cylindrical cells. More frequently, however, they represent formations resulting from the cystic degeneration of neighboring ovarian follicles or of adenomatous new-growths. The ovary may be entirely destroyed by

the dermoid; but remains of its tissue are often present (*k*). In very rare cases several dermoids may develop coincidently in one ovary; a double-sided occurrence is seen in about fifteen per cent. of all cases. Ovarian dermoids are observed most frequently in individuals of middle age, but occur also in children.

The most characteristic feature of ovarian dermoids lies in the fact that they contain *elements of all three germ-layers,* and that a certain law in the arrangement of the different elements is observed. The derivatives of the ectoderm and mesoderm, in particular the skin and its appendages, also bone and teeth, and often brain substance, are developed to the most marked extent; while entodermal formations, cylindrical-celled tubules, and mucous glands are ordinarily developed to a much less degree, and lie concealed in the deeper parts of the growth. The structure of the growth as a whole gives the impression of a *rudimentary embryo* with an unequal development of ecto- and entodermal tissue, and such tumors have therefore been appropriately designated as **embryomata** (Wilms).

The **solid teratomata** of the ovary are much more rare than the dermoid cysts. They form tumors which are composed of a confused mixture of the most varied tissue-formations, viz., epidermis, epithelial pearls, hairs, sebaceous glands, sweat-glands, tubules, and cysts lined with ciliated epithelium, acinous glands, connective tissue rich in cells, adipose tissue, muscle, cartilage, and bone. In rare cases teeth, intestine, thyroid and brain tissue of a rudimentary character may be present.

Since these formations also contain *elements of all three germ-layers,* and are distinguishable from the dermoids only through the lack of any regular order of arrangement of the different tissues, and through the more rudimentary development of the individual tissues, they may likewise be classed with the **embryomata.** With reference to their lack of any structural organization approaching that of the human embryo, Wilms has designated these formations as *embryoid tumors.*

Since the embryoma contains elements of all three germ-layers, in part in orderly arrangement, the genesis of such a tumor may be explained by the assumption of a *development from an ovum.* Bonnet regards it as probable that either in the development of a fertilized ovum, in the early stages of division, a blastomere (or several) may be delayed in division and later give rise to an independent formation containing elements of all germ-layers, or that (Marchand) a fertilized polar body (the fertilization of the polar body has been demonstrated in vertebrates) finds its way between the blastomeres of a developing ovum, and later develops within the embryo. The first assumption seems more probable, and the embryomata of the ovary may consequently be regarded as *rudimentary unioval twin malformations* (§ 128), which are to be placed in the same category with the fœtal inclusions of other organs. The fact that the ovaries (and testicles) form the favorite seats of such growths is probably dependent upon the fact that the urogenital anlage in its earliest stage forms relatively such a large part of the embryonal anlage (Bonnet), or that the blastomeres, from which the sexual glands later arise, more easily than others take on an especial development, that may lead to the formation of a rudimentary twin.

The **teratomata of the testicle** occur most frequently in forms which according to their structure are designated as *adenocystoma, chondro-adenoma, chondrosarcoma, adenomyosarcoma, cystosarcoma, cystocarcinoma,* etc. In some cases the formation of cysts with fluid contents forms

the most striking feature of the tumor (Fig. 326); in other cases cysts are found only in certain parts of the growth; and, finally, in still other cases the tumor may be solid throughout. These growths may reach the size of a child's head. They may be congenital, but develop more frequently in adult life, and then grow rapidly.

The lining of the cysts is, as a rule, of entodermal character, but may vary in one and the same cyst (Fig. 369). Simple cubical (Fig. 369, *b*) and cylindrical epithelium either with or without cilia, as well as stratified ciliated epithelium (*d*) and pigmented epithelium (*e*), may be found.

Ectodermal tissue is present only in scanty amount, and is limited to pigmented epithelium or to scattered groups of cells showing cornification; or it may be entirely absent, or, at all events, cannot be demon-

FIG. 369.—Congenital adenocystoma (teratoma) of the testicle with pigmentation and formation of cartilage (Müller's fluid, hæmatoxylin). *a*, Connective-tissue stroma; *b*, simple cubical epithelium; *c*, stratified cylindrical epithelium; *d*, stratified ciliated cylindrical epithelium; *e*, pigmented epithelium lining gland-tubule; *f*, pigmented connective-tissue cells; *g*, cartilage in connective tissue; *h*, cartilage lying in a gland-tubule. (Section taken from tumor pictured in Fig. 336.) × 100.

strated in the case of tumors of large size. Besides the cysts, mucous glands may also be found.

Of the connective-tissue substances, fibrous tissue, myxomatous tissue, cartilage (Fig. 369, *g*, *h*), and occasionally also muscle (Fig. 370, *a*), fat tissue, and more rarely bone, are present.

According to investigations by Schlagenhaufer, Wlassow, Risel, and others, the teratomata of the testicle may also contain tissue-formations corresponding in their structure to the malignant chorio-epitheliomata, characterized in particular by syncytial formations.

Teratomata of the character of **dermoids**, containing, as in the case of the ovarian dermoids, such structures as skin, brain tissue, cranial and tracheal tissues, and more rarely teeth and structures resembling the eyes, are of rare occurrence in the testicles, but are found both in children and in adults.

To what extent the different teratomata of the testicles are to be classed with the **embryomata**, or to what extent they can be explained

FIG. 379.—Teratoma (adenomyosarcoma) of the testicle (formalin, hæmatoxylin, eosin). *a*, Cellular tissue with bands of muscle; *b*, gland-tubule. × 100.

by the assumption of tissue-implanations at later stages of embryonal development, cannot at present be determined. When elements of all the germ-layers are present in the tumor, the assumption is justified that the growth belongs to the embryomata or embryoid tumors, and has arisen in the same manner as has been assumed in the case of the ovarian dermoids. The occurrence of syncytial formations speaks in favor of this assumption. The presence of single tissue-formations—as, for example, of cartilage or of muscle—in tumor-formations of a more simple character, may be explained by the assumption that such tissues find their way into the anlage of the testicle during the period of embryonal development.

The *proliferations of chorio-epithelial character* found within teratomata of the testicles are believed by *Schlagenhaufer* to depend upon the development of fetal membranes, and he regards the myxomatous tissue present in such tumors as representing the chorionic stroma. According to *Marchand* and *Risel*, they are to be regarded only as products of the fetal ectoderm having the same histogenetic significance as the other ectodermal structures of the teratoma. It is yet to be determined to what extent corresponding ectodermal formations occur in teratomata of other organs. *Pick* found them in a teratoma of the ovary in a nine-year-old girl. Further, it is to be noted that syncytial formations occur in tumors (angiosarcoma, endothelioma) that have nothing to do with fetal ectoderm. It cannot, therefore, be regarded as positively determined that the syncytial formations in teratomata of the testes actually correspond to a chorio-epithelioma. *Wlassow* believes that the chorio-epitheliomatous proliferations observed by him in tumors of the testis, and designated by him as syncytioma

yncytiomatodes, are to be regarded as derivatives of incompletely developed epithelium of embryonal gland tubules.

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See also §§ 126 and 128.

§ 128. **Teratoid cysts of a complicated structure and solid teratomata** are found, outside of the sexual glands, in the same regions as the simple teratoid cysts, but show a particular predilection for the region of the coccyx. The complex character of the *cysts* is shown by the presence in the cyst-wall of cartilage, bone, fat tissue, mucous glands, smooth and striped muscle fibres, nerve-tissue, and tissue of a sarcomatous or carcinomatous nature. Dermoid cysts may also contain teeth, and further also ciliated epithelial cysts. The *solid teratomata* occur, in the first place, as *hairy polypi* (nose, throat, and mouth)—that is, as polypoid tumors covered with hairy skin, and consisting essentially of adipose tissue, which may also contain muscle fibres, cartilage, bones, teeth, and cysts. Another group consists of those *kidney-tumors* which, in addition to tubular glands, inclose sarcomatous tissue, cartilage, fibrous tissue, adipose tissue, and muscle tissue, in rare cases also ectodermal tissues.

In the *vagina* and *cervix uteri* of children there occur tumors, for the greater part of a racemose character, which, in addition to connective tissue, myxomatous tissue, round and spindle-celled tissue, also contain smooth and striped muscle-fibres, and in rare cases also cartilage. Finally, there occur tumor-like growths of a very complicated structure in the *cranium, thorax, abdomen, urinary bladder, neck, lower jaw,* and especially in the region of the *coccyx*. They contain the most varied forms of tissue: connective tissue, adipose tissue, cartilage, bone, gland tissue, muscle, nerve and brain substance, as well as ectodermal and entodermal cysts. They may further inclose rudimentary, or completely formed, or at least easily recognizable, portions of the body.

Both the complex teratoid cysts and the solid teratomata are in many cases to be regarded as **local disturbances of development** characterized by a **misplacement of tissue** or a **separation of tissues** by **constriction within a single individual** (*monogerminal tissue-implantation, autochthonous teratoma*). The hairy polypi of the throat, the cystic or solid teratomata at the base of the skull or in the hypophysis may be explained by the assumption of a misplacement of ectodermal tissue. The presence of cartilage and mucous glands in teratoid cysts of the mediastinum may be explained by the proximity of the trachea. The teratoid mixed tumors of the kidney may be explained by the assumption that in the kidney region, in addition to kidney-tubules and remains of the Wolffian body, products of the mesenchyma arising from the myotome may undergo proliferation. The occurrence of squamous-celled formations in such tumors must depend upon the fact that ectodermal tissue has found its way into the kidney anlage. The presence of striped muscle-fibres of cartilage in tumors of the vagina and uterus is explainable by the assumption of an implantation of myotome or of anlage of the vertebræ (sclerotome); but many writers hold the opinion that striped muscle may be formed from unstriped. Wilms believes that the Wolffian duct and its development give occasion to and are the cause of the implantations into the cervix and vagina. In the case of the teratomata of the coccygeal region the manifold character of these growths may be explained by the fact that portions of the terminal vertebræ, of the pelvis, and of muscular tissue, as well as remains of the neuroenteric canal, the hind-gut, and the medullary canal, take part in the formation of the tumor. In the intracranial teratomata, as well as in the simple dermoids, tissue-implantations probably form the basis for the growth. Moreover, there exists indeed the possibility of another mode of origin for these growths—namely, the presence of a **rudimentary twin,** a *bigerminal implantation*. Such an assumption is well founded in all those cases in which the teratoma contains fully developed or rudimentary parts of the body, or tissue-formations which cannot be explained by the assumption of a misplacement of the tissue elements of a single fœtus at the spot in question. Ekehorn regards the complex dermoids of the mediastinum, which contain skin, cartilage, bone, and the constituents of mucous membranes, as bigerminal implantations. Lexer emphasizes such a mode of origin for the teratoid mixed tumors of the abdominal cavity (see §§ 127, 131, and 147).

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See also §§ 126 and 147.

CHAPTER IX.

Disturbances of Development and the Resulting Malformations.

I. General Considerations Regarding Disturbances of Development and the Origin of Malformations.

§ 129. After the copulation of the sexual nuclei has taken place, the development of the embryo proceeds by a progressive division of nuclei and cells, associated with which there arise in an orderly manner especial groupings of cell-complexes and differentiation of the same into especial tissues and organs. The multiplication of the cells, as well as the development of individual cell-groups into especial organs and parts of the body, depends upon intrinsic causes, and is controlled by the characteristics which the embryo has received through the transfer of the inheritable paternal or maternal characteristics at the moment of the union of the sexual nuclei, which are to be regarded as the carriers of inheritable characteristics. It follows, therefore, that the characteristics of the species as well as the especial peculiarities of the given individual are in general already predetermined in the germ, and the development of the embryo proceeds essentially under the control of innate moulding forces. Nevertheless, this development is not accomplished without the influence of environment, in that the embryo of necessity receives its nourishment from the maternal organism, and at the same time is exposed to mechanical influences on the part of its membranes and of the uterus. These influences may therefore operate to modify the development of the fœtus.

In every species of animal, man included, both the bodily form and the configuration of the organs present a *particular type*, which experience has shown constantly to recur, and which is therefore looked upon as normal. If more or less marked departures from this type occur, which can be referred to a more or less marked abnormal course of the intra-uterine development, the condition is designated as a **congenital malformation.** When the departure from the normal structure is very marked, so that the affected individual is grossly malformed, it is spoken of as a **monster.**

According to common usage, the term malformation is usually applied only to anomalies in the form of the body as a whole, or to single parts of it which present to external inspection rather striking departures from the normal. It is nevertheless entirely correct to use this term for pathological conditions of intrauterine origin, which consist not so much in an abnormal change in form, but rather in an incomplete or faulty organization of the affected part or organ.

A malformation affecting a single individual is known as a **single malformation** or **single monster**; one made up from two individuals is termed a **double malformation** or **double monster.**

Malformations may owe their origin to either intrinsic or extrinsic causes.

As **intrinsic causes** may be considered all such as already exist in the germ, so that in the development of the embryo malformations may arise spontaneously without the aid of extrinsic influences. When such a malformation occurs for the first time in a family, it must be regarded as a *primary germ-variation*. This may be explained in one of two ways: either one or both of the sexual nuclei entering into union may have been abnormal, or both may have been normal, but from their union a variety has arisen which from one point of view is to be regarded as pathological (cf. § 17). It is also possible that disturbances in the processes of fertilization can give rise to pathological variations.

If a similar malformation has already occurred in the parent, the case may be regarded as one of *inheritance*. If the malformation appearing is a peculiarity which was not present in the parents, but did show itself in more remote ancestors, while wanting in the intermediate links, the phenomenon is designated as *atavism*.

FIG. 371.—Malformation of the head, due to adhesions of the membranes to the frontal region (firm adherence of placenta to uterus). *a*, Membranous sac inclosing a vascular, spongy tissue containing numerous cysts; *b*, eye; *c*, lip; *d*, funnel-shaped depression lined with mucous membrane; *e*, left, e_1, right ala nasi; *f*, connective-tissue bands. Reduced one-fourth.

As primary germ-variations appear the same malformations which are also inheritable—that is, only those malformations are inheritable which origially appeared as primary germ-variations. To such inheritable malformations belong the increase in the number of the fingers and toes (polydactylism), malformations of the hands and feet, abnormal hairiness, harelip, and certain pathological conditions of the nervous system, as, for example, multiple fibromata of the peripheral nerves.

Under **extrinsic causes** of malformations are to be considered especially *concussion, pressure, disturbances in the supply of oxygen and nourishment*, and *infections.*

Concussions of the uterus may in all probability directly damage the embryo at a very early stage. At a later stage of development the harmful effects of trauma are probably more often to be sought in a tearing loose of the egg and in decidual hæmorrhages, whereby the nourishment of the embryo is disturbed. It is evident that hæmorrhages from other causes, also changes in and contaminations of the maternal blood, as in infections, and, further, pathological conditions of the uterus itself,

may have a harmful influence upon the developing egg; yet all these conditions probably lead more often to the death of the fœtus and the expulsion of the egg than to the development of a malformation. Infectious diseases of the mother may be transmitted to the fœtus and give rise to their characteristic changes in the latter. An abnormal pressure from the uterus or its membranes may be exerted upon the embryo, especially when there is a deficient amount of amniotic fluid; and malformations of the extremities (Fig. 374), in particular, not infrequently show evidences of pressure having been exerted.

FIG. 372.—Malformation of the face, caused by amniotic adhesion and pressure. Asymmetry of the face. *a*, Malformed nose; *b*, b_1, rudimentary lid-clefts; *c*, c_1, clefts in the upper lip and alveolar process of the upper jaw; *d*, intermaxillary bone with prominent lip; *e*, oblique facial fissure closed by scar tissue so as to form a groove.

From the anatomical findings in many malformations it appears that **pathological conditions of the amnion** may exert a damaging influence upon the embryo and give rise to different forms of malformations.

This may be brought about through *abnormal adhesions between the embryo and the amnion*, as well as by *pressure of the amnion upon the embryonal anlage*. Even at the birth of the child adhesions in the form of bands and threads (Figs. 371, *f*; 373) may not infrequently be demonstrated, and their connection with the malformed parts is such as to leave no doubt that they stand in a causal relation to the malformation. Such adhesions may give rise to severe malformations of the cerebral (Fig 371) or of the facial (Fig. 372) portions of the head. Not infrequently portions of the extremities are snared off by amniotic bands (Fig. 373), and may be completely amputated and then absorbed.

To what extent these adhesions of the amnion with the fœtus are to be referred to primary adherence and intergrowth, and to what extent to inflammatory processes of later occurrence, is yet a disputed question. Not infrequently the adhesions at birth are no longer visible and the affected part presents only a scar-like appearance (Fig. 372).

According to Dareste and Geoffroy St.-Hilaire, an abnormal tightness of the amnion may easily exert a harmful influence upon the embryo. An abnormal closeness of the cephalic cap of the amnion may cause the malformations known as anencephalia, exencephalia, cyclopia, and cebocephalia or arrhincephalia (§ 134); while an abnormal tightness of the caudal cap may give rise to sirenomelia (§ 138). Further, the cleft malformations of the anterior abdominal and thoracic walls (§ 136) are also associated with a faulty development of the amnion; still the latter condition is often not so much the cause as it is a concomitant of the malformation, which may be the result of a variety of causes, and, indeed, is often to be regarded as a spontaneous or primary malformation.

The period at which the injurious influence is active varies greatly, and consequently so does the extent of the damage done by it. The earlier the damage occurs, the greater the extent of the injury. Malformations in the narrower sense of the term arise chiefly during the first three months, during the period when the body and its individual parts are developing their proper forms. Damage to the fœtus at a later period occasions *changes which are more closely allied to those acquired after birth.*

Some malformations are **typical**—that is, they always appear in the same form; while others again are wholly **atypical,** so that the most astonishing anomalies of form may arise. The latter are for the greater part the result of extrinsic harmful influences operating secondarily, while the former may be regarded as owing their origin chiefly to intrinsic causes, although external influences may also cause typical malformations.

Geoffroy St.-Hilaire ("Hist. gén. et partic. des anomalies de l'organization chez l'homme et les animaux," Paris, 1832–37) discards entirely the teaching of a primary abnormality of the germ (*Haller* and *Winslow*), and attributes arrests of development purely to mechanical influences. *Panum* ("Untersuch. über die Entstehung der Missbildungen," Berlin, 1860) agrees with him on the whole, although he admits the possibility of a primary abnormality. He produced malformations in hens' eggs by means of temperature variations and by varnishing the shells. *Dareste* ("Recherches sur la

FIG. 373.

FIG. 374.

FIG. 373.—Hand stunted by amniotic adhesions; ring-finger snared off; middle and index fingers grown together and distorted. Reduced one-sixth.

FIG. 374.—Hand stunted and deformed by pressure; thumb absent; hand flattened; great bending and shortening of the forearm. Reduced one-fifth.

production artificielle des monstruosités," Paris, 1877) made similar experiments and produced malformations due to arrested development by keeping the eggs in a vertical position, by varnishing the shells, by raising the temperature above 45° C., and also by irregular warming of the eggs.

Very recently *L. Gerlach*, *Fol*, *Warynsky*, *Richter*, *Roux*, and *Schultze* have in particular carried on experiments in this line, and have attempted, with partial success, to

produce malformations in chicken-embryos through the localized influence of radiant heat, variations of temperature, varnishing the eggs, changes of position, injuries, removal of a portion of the white of the egg, and by agitation. *Roux*, experimenting on frogs' eggs, found that, after destruction of one of the first segmentation-spheres, the other continued to develop and formed the half of an embryo, thus demonstrating that each of the first two segmentation-cells, corresponding in their position to the right and left body-halves, contains within itself the anlage material for the corresponding half of the body. But since the body-half which is wanting may later be replaced by subsequent development from the undestroyed half, and a whole structure be produced, each half must also possess the power of producing also the other half. According to investigations by *Herlitzka*, *Driesch*, *Morgan*, *Wilson*, and others, the first two or even the first four segmentation-cells in tritons, teleosts, ascidians, and echinoderms possess the power of forming an entire embryo.

Schultze experimented on the eggs of amphibia; these normally always assume such a position that the darkly pigmented protoplasmic substance of lighter specific gravity lies above, the heavier clear protoplasm rich in yolk granules lies below. By placing the eggs in an abnormal position and preventing their return to the normal position malformations may be produced, the degree of malformation standing in direct relation to the size of the angle formed by the line of gravity and the abnormally-placed axis of the egg. By turning the egg through an angle of 180° in the two-cell stage a double monster is regularly produced. The same turning in the eight-cell stage causes a complete cessation of development. These disturbances arise from displacements consequent upon the sinking of the heavier and a rising of the lighter constituents of the egg.

According to investigations by *O. Hertwig*, the eggs of axolotl, when kept in a 0.7-per-cent. solution of sodium chloride, undergo a pathological development, which is confined to the central nervous system in the region of the head and trunk. If frogs' eggs are left before fertilization for one to four days in the uterus of the dead female and are then fertilized, there are formed, besides normal embryos, various malformations due to defective development, for example, spina bifida.

Recent studies have shown that monsters and malformations may be produced by Roentgen irradiation of fertilized ova or of either ova or spermatozoa before fertilization. *Gilman* and *Baetjer* found that the eggs of amblystoma developed abnormally under Roentgen irradiation, the embryos showing no mouths. Chicks developed in exposed eggs presented malformations of the occipital region and extremities and in the distribution of the feathers. *Bardeen* found that in frogs injury to the spermatozoa by Roentgen rays caused the development of monsters from eggs fertilized by such damaged spermatozoa.

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§ 130. **Single malformations** may be conveniently divided into five groups, according to the kind of change which characterizes them.

As **arrests of development** or **monsters due to defective development (monstra per defectum)** may be classed in the first place all those malformations in which the whole or a part of the body is abnormally

small and imperfectly developed (*hypoplasia*), and also **those malformations** characterized by the complete absence or very **great stunting** (*agenesia* or *aplasia*) of individual organs and parts of the body.

If, in the case of parts or organs of the body which are normally formed by the union of anlage which are originally separated, such union should fail to take place as the result of a primary or secondary disturbance of growth, the arrest of development may show itself in the form of *clefts* and *reduplications*. Thus, for example, imperfect development of the plates forming the anterior body-wall gives rise to clefts in the median line of the thorax and abdomen; a failure of union of the maxillary processes of the first branchial arch with each other or with the nasal process of the frontal bone gives rise to clefts in the face. Defective union of the bilateral portions of the female genital tract results in a more or less extensive reduplication of the uterus or vagina.

When the anlage of two organs lie near to each other, these may under certain conditions become united so as to produce a *coalescence* or *adhesion* between two organs or parts which should normally be separated. For example, the kidneys at times may be more or less united, and the eyes may be more or less completely merged into a single organ.

Malformations due to excessive growth (monstra per excessum) are characterized in part by *abnormal size* of individual parts, and in part by an *increase in number* of the same. For example, an extremity or a portion of one, as a finger, may reach an abnormal size (*partial giant growth*), or the whole body may be involved in the abnormal growth (*general giant growth*). An increase in number occurs particularly in the case of the mammary gland, spleen, adrenals, and fingers. Additional glandular organs are designated *accessory* or *supernumerary organs*.

As **malformations due to an abnormal disposition of organs (monstra per fabricam alienam)** are designated by Förster certain anomalies of the internal organs of the thorax and abdomen, which are characterized by an abnormal position of the organs, and in part also by changes in the relation of individual parts to each other. In this class belongs the condition known as *situs transversus*—that is, the transposition of the thoracic or abdominal organs, or of both. Further, various *defects in the heart and great vessels* may also be classed here, though it should be noted that these are more properly regarded as *arrests of development*.

A fourth group of malformations includes those characterized by **displacement of tissues** and by the **persistence of fœtal formations**, as already mentioned in §§ 126 and 128.

Finally, as a fifth group may be classed those **malformations exhibiting a mixture of the sexual characteristics**, known as *true* and *false hermaphroditism*. True hermaphrodites possess both male and female sexual glands; false hermaphrodites are unisexual, but the remainder of the sexual apparatus does not correspond to the sexual gland, or there is a simultaneous formation of organs belonging to both the male and female. A part of these malformations are arrests of development: others are to be regarded as cases in which from the original bisexual anlage the organs of both sexes have developed, whereas normally the anlage of one sex undergo a retrograde change instead of developing, and persist only in a rudimentary form.

§ 131. **Double monsters (monstra duplicia)** are malformations consisting of two individuals; if both twins are developed (*symmetrical twins*) they are always of the same sex and are united to each other in the same portions of the body; the duplicated portions are usually equally developed (*equal*), but *unequal* forms also occur in which one twin

is stunted in its development. *Asymmetrical* forms also occur in which one twin remains wholly rudimentary and is dependent upon the other for its nutrition (*parasitic double monster*). Often it is *implanted* in the other or included within it (see § 127).

All double monsters arise from **one egg** *and have a common chorion.* In the formation of *symmetrical double monsters* two separate embryonal anlage are probably formed from one germinal vesicle, and these in their growth blend with each other to a greater or less extent, but a duplication or a splitting may also occur within a single anlage, and this process occurs particularly in the anterior reduplications which can also be produced experimentally in animals. The genesis of the rudimentary *asymmetrical twins* occurs chiefly in the manner described in § 127 (Teratomata).

The *causes of a duplication of the embryonal anlage in a single germinal vesicle* are not known. According to *Fol*, double and multiple monsters arise through the abnormal impregnation of an ovum with two, three, or more spermatozoa; but other observations (*Born*) indicate that ova fertilized by two or more spermatozoa do not develop. According to *Marchand*, the doubling of the anlage is to be referred to conditions existing before the beginning of segmentation, either to conditions within the egg before fertilization, or to the fertilization itself. *Wiedemann* and *Wetzel* hold the opinion that the origin of double monsters dates from the moment of impregnation, and is due to the fertilization of ova containing two germinal vesicles by two spermatozoa.

Gerlach produced double monsters (anterior duplication) from hens' eggs by varnishing these before incubating, leaving free only a Y-shaped spot in the region of the primitive streak. Inasmuch as he only rarely succeeded in obtaining such results, it is possible that these malformations, which not infrequently occur in chickens, were accidental. *Schultze* obtained double monsters by turning frogs' eggs during the two-cell stage through an angle of 180° (cf. § 129). *Spemann* was able to produce double-headed embryos of tritons by constriction of the embryonal anlage before the closure of the medullary plate to form the medullary groove; also by a median constriction in the two-celled- and blastula-stage. *Born* succeeded in uniting together portions of the larvæ of amphibia, not only of the same kind, but also of different species, genera, and families (*Rana esculenta* with *Bombinator igneus*, and with *Triton*). The conditions were most favorable for union in the case of larvæ of about 3 mm. length. Not only the external coverings of the body, but also the anlage of organs (liver, intestine, heart-tube), were blended into a united organ, the union being completed through specific tissue of the same kind. From all these experiments the conclusion may be drawn that double monsters may be produced from a normal egg through secondary influences, and that neighboring embryonal anlage may grow one into the other. On the other hand lies the possibility that especial conditions within the egg before fertilization may be the cause of the duplication. According to *Schultze*, this may possibly lie in the presence of two nuclei or of two spindles, or in an over-ripe condition of the egg with a tendency to fragmentation into two halves, which divide shortly before fertilization. Therefore a normally fertilized ovum in the two-cell stage may be brought through some influence (as in the experiment of *Schultze*) to the formation of two individuals.

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See also § 129.

II. The Different Forms of Malformations in Man.

I. Arrests of Development in a Single Individual.

(a) *Arrest of the Development of the Entire Embryonal Anlage.*

§ 132. An **arrest in the development of the entire embryonal anlage** manifests itself in two ways. If the disturbance is very marked, a **further development of the embryo is impossible**, and it either dies at once or becomes stunted, and after a certain time perishes. If the disturbance is less severe there develops a normally formed fœtus, but it remains small and stunted—that is, a **dwarf is formed** (**nanosomia** or **microsomia**).

A **dead fœtus** is in the majority of cases expelled together with its membranes (**abortion**). In other cases in which the embryo for some cause or other remains stationary in development, the egg may remain for weeks or even months in the uterus and increase in size, so that there arises a disproportion between the size of the embryo and of the egg. According to His, the first changes *after death* are shown in a marked swelling of the central nervous organs, leading to changes in the configuration of the head. Later there occurs an infiltration of the tissues with wandering cells, the boundaries of the organs become indistinct, the entire **embryo** becomes cloudy and soft, the superficial structure indistinct, and the embryo finally becomes **completely dissolved**. According to Berlet and Engel, the wandering cells infiltrating the tissue arise in the embryo itself, and indeed from its own blood.

When a fœtus well advanced in development dies and remains within the maternal organism there may result the formation of **a lithopædion**. This occurs most frequently in the abnormal situation of the ovum known as extrauterine pregnancy, in which the embryo lies in the peritoneal cavity, in a tube, or in an ovary. If the fœtus dies at such an advanced stage of development that it cannot be absorbed, it may be carried within the maternal organism for years. Not infrequently its form is perfectly

preserved (Fig. 375), and the whole fœtus becomes inclosed in a connective-tissue membrane. In other cases the fœtus, in the course of time, becomes converted into a partially fluid mass, which contains the osseous remains, as well as fat, cholesterin, and pigment, and is surrounded by a fibrous capsule. Lime-salts are usually deposited both in the newly formed membranes as well as in the portions of the fœtus remaining, and for this reason the fœtus is known as a "stone-child" or "petrified child."

FIG. 375.—Lithopædion, entirely inclosed in connective-tissue membranes (removed from abdominal cavity by operation two years after beginning of pregnancy). Extrauterine pregnancy caused by embryo breaking through the uterine portion of a tube into the abdominal cavity. Reduced to one-third.

According to the condition of the fœtus there may be distinguished three chief forms of lithopædion (Küchenmeister). In the first the mummified fœtus may be easily shelled out from the calcified membranes (*lithocelyphos*). In the second form the fœtus becomes adherent to the membranes at various points which become calcified, while the other portions become mummified (*lithocelyphopædion*). In the third form the fœtus is discharged, through the rupture of the membranes, into the peritoneal cavity, and later becomes encrusted with lime-salts (*lithopædion* in the narrower sense).

The long retention of a ripe or even older fœtus within the uterus (*missed labor*) is rare, but may occur (1) in an accessory horn of the uterus, (2) in interstitial pregnancy, (3) after rupture of the uterus.

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(*b*) *Defective Closure of the Cerebrospinal Canal and the Accompanying Malformations of the Nervous System.*

§ 133. **Defective closure of the vertebral canal** leads to the malformations known as **rachischisis** or **spina bifida.** If the defect in the vertebral column is open so that at the bottom of the cleft the bodies of the vertebræ covered by membrane are seen, the malformation is ordinarily termed *rachischisis*. When, at the site of the defect, there is seen a protruding sac, the malformation is usually designated *spina bifida*, or more correctly *spina bifida cystica;* though to this formation the names *rachischisis cystica* or *hydrorachis cystica* may also be applied.

In **rachischisis totalis** (*holorachischisis*) (Fig. 376) the bodies of the vertebræ form a shallow groove opening posteriorly, and usually covered by a thin, transparent membrane; in rare cases rudiments of the spinal cord are still present in the form of whitish bands and lines. In this manner there occurs a **total** or **partial amyelia.** The defect involves principally the motor tracts and centres, as well as the columns of Clarke and the lateral cerebellar tract, while the spinal ganglia are developed (Mauz, Leonowa, K. and G. Petrén), and may send sensory fibres into the membranous masses of the spinal groove.

The delicate membrane which lines the furrow and covers the dura mater lying beneath it upon the bones is the ventral portion of the spinal pia mater. A part of the nerve-roots may have undergone development, arising either from rudiments of the spinal cord or from spinal ganglia.

Partial rachischisis (*merorachischisis*) involves usually the sacrolumbar or the upper cervical region, while the intervening portions of the vertebral column are only rarely the seat of malformations. The dorsal surfaces, with the overlying dura and pia mater, of the bodies of the vertebræ whose arches remain rudimentary are covered for the greater part by a mass of velvety vascular tissue, which contains rudiments of the spinal cord (the *area medullo-vasculosa*, von Recklinghausen), though the amount of this tissue may be very small or may even be wholly wanting. To the outside of this tissue layer, which is not everywhere equally abundant and which diminishes at the sides, there comes next a delicate, transparent, vascular membrane which represents the continuation of

the pia mater covered with epithelium (*zona epithelio-serosa*); and next, outside of this, a zone of epidermoidal tissue somewhat thinner than normal skin, and often covered with many hairs (*zona dermatica*), separating the reddened central area from the normal skin.

FIG. 376. Craniorachischisis with total absence of the brain and spinal cord. The base skull is covered with ragged membranous masses, the open spinal furrow with a delicate membrane (pia mater). Kypholordotic curvature and shortening of the spinal column. Reduced one-sixth.

Spina bifida cystica or **rachicele** (*rachischisis cystica*) occurs in three chief forms: *myelomeningocele, meningocele,* and *myelocystocele.* According to its site there may be further distinguished a cervical, dorsal, lumbar, lumbosacral, and a sacral spina bifida. In general, a spina bifida is characterized by the development of a fluctuating tumor, which is in most cases visible externally (Fig. 377) on the posterior aspect of the

FIG. 377.—Spina bifida sacralis. (After Froriep and Förster.) Girl of nineteen years, born with a tumor the size of a pigeon's egg over the upper sacral and lower lumbar regions, which enlarged from the sixth year on, while at the same time club-feet developed

spinal column (*spina bifida posterior*); but instances also occur in which the sac projects anteriorly from the spinal canal (*spina bifida anterior*), and others in which it is so small that it is covered with normal skin and is not visible externally (*spina bifida occulta*).

Myelomeningocele appears most frequently as a *spina bifida lumbo-*

sacralis, and usually forms a tumor varying in size from that of a nut to that of an apple and increasing in size after birth, in the region of the lower lumbar and upper sacral vertebræ. It is covered either by smooth or scar-like skin, or may be devoid of skin on its summit and there covered by a reddish, mucosa-like tissue (area medullovasculosa). The portion uncovered by skin may be drawn in, like a scar. In rare cases there may be no external tumor (*spina bifida occulta*), the site of the cleft being indicated only by a more marked growth of hair or by a depression.

On opening the sac, which is composed of the arachnoid (Fig. 378, *e*) and the pia (f, f_1), while the dura (g) does not extend over the dorsal portion of the sac, it may be seen that the lower end of the spinal cord (b_1) is drawn outward, and that the cavity of the sac is crossed by nerve-roots (i, i_1). Occasional nerve-roots (h) may also spring from the columns of the cord (b_1) in its course through the sac.

According to these findings there is, therefore, an accumulation of fluid in the meninges, a *hydromeningocele* (hydrorachis externa circumscripta), which is combined with a prolapse of the spinal cord, a *myelocele.* At the site of the protrusion the vertebral arches are defective, and this defect may reach as far as the hiatus sacralis. Smaller defects may involve only one or two vertebræ.

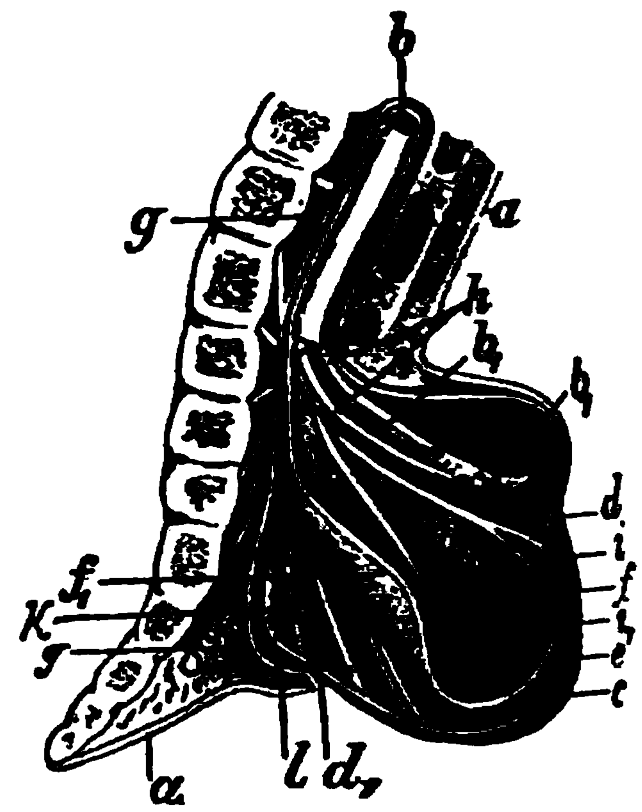

FIG. 378.—Myelomeningocele sacralis in sagittal section, a little to the left of the median line. (After von Recklinghausen.) *a*, skin; *b*, b_1, spinal cord; *c*, area medullovasculosa; *d*, cranial, d_1, caudal polar groove; *e*, arachnoid; *f*, pia, somewhat separated from the arachnoid; f_1, portion of pia mater turned over; *g*, dura mater; *h*, recurrent roots of the fourth lumbar nerve; *i*, radix anterior; i_1, radix posterior of the fifth lumbar nerve, running free through the arachnoidal sac; *k*, sacral nerve-roots between the arachnoid and pia; *l*, filum terminale.

Dorsal and *cervical meningoceles* are much more rare than the lumbosacral. The defect in the vertebral arch is usually confined to one or two vertebræ. The spinal cord is here involved in the meningocele in so far that portions of it are drawn outward in the form of a band or cone.

Hydromeningocele spinalis arises from a hernial protrusion of spinal arachnoid due to a localized collection of fluid in the subarachnoidal space. It may occur in the first place at the upper end of the spinal column in the case of a cleft of the upper cervical vertebræ, at the same time with hernia of the brain in the occipital region. More frequently, however, it occurs in the sacral region, where the hernial protrusion takes place either through a defect in the vertebral arches and bodies or through the hiatus sacralis, or between vertebral arches or through intervertebral foramina. In the majority of cases the dura takes no part in the formation of the sac, but views differ upon this point, and by many writers (Hildebrand) a dural sac is described. Through a progressive accumulation of fluid the sac may attain a very large size. Small meningoceles may be concealed in the deep tissues.

According to the direction of the hernial protrusion there may be distinguished a *meningocele posterior* and a *meningocele anterior*, the latter taking place through a defect in the bodies of the vertebræ (*rachischisis anterior*).

Myelocystocele or **hydromyelocele** (*syringomyelocele*) takes its origin

in a dilatation of the central canal of the spinal cord, as a result of which a larger or smaller portion of the cord with its connective-tissue envelopes becomes converted into a cystic tumor. The dura is usually wanting over that portion of the sac protruding from the vertebræ.

According to von Recklinghausen, the wall of these sacs is formed essentially of the inner spinal meninges, but is lined on the interior by a cylindrical epithelium, and has at some part of its inner surface an area medullovasculosa—usually on the ventral side, rarely on the dorsal. Corresponding to this condition the roots, in case they are still preserved, spring mostly from the ventral, rarely from the dorsal outer wall of the sac. The cavity itself is crossed neither by bands nor by nerves.

Myelocystoceles occur, in the majority of cases, in lateral clefts of the vertebral column. They show ~~a tendency to be combined with *defects*~~ and *asymmetries of the bodies of the vertebræ,* and thereby often with *shortenings of the trunk,* which at times affect only the dorsal region, at other times also the lumbar region. Very frequently there exists at the same time an exstrophy of the abdomen, bladder, and intestine.

Myelocystoceles are mostly covered only by the outer skin, but are sometimes concealed deep down in the soft parts. They may further be combined with a meningocele, so that a **myelocystomeningocele** arises.

In cases of rachischisis there sometimes occurs a **division of the spinal cord into two parts** (*diastematomyelia*), most often in the case of a total rachischisis, in which indeed the rudiments of the spinal cord are usually only indicated. In partial rachischisis such division is more rare, but the separated strands of spinal cord are better developed, and the fibrous and bony coverings may, at the beginning or end of the cleft, send dividing septa between them. Cases have occurred in which each cord-half possessed an H-shaped area of gray matter.

In the earliest embryonic period the medullary groove is formed by the development on both sides of the median line of wall-like elevations of the ectoderm which are designated as the medullary folds. Through the converging growth and union of the latter the medullary groove is closed and formed into the medullary canal. Thereupon the cell-masses (primitive vertebral plates) lying at the sides of the newly formed canal form an envelope about it, which gives rise in the first place to a membranous, non-articulated vertebral column. In this, at the beginning of the second month, there arise discrete cartilaginous areas from which, in the course of further development, the vertebral bodies and arches are formed, while between them the intervertebral discs and vertebral ligaments appear. The development of the cartilaginous vertebræ is not completed until the fourth month, and up to this time the dorsal covering of the medullary tube consists of the united portions of the membranous vertebral column. The cartilaginous constituents of the vertebræ are in the course of development replaced by bone.

The *origin of rachischisis* is to be referred to agenesia and hypoplasia of the medullary folds, which should form the medullary groove of the vertebral arches. The agenesia of the spinal cord is also to be dated from the very earliest period. Whether it is a primary agenesia predetermined in the germ, or whether extrinsic injurious influences, perhaps toxic substances (*Hertwig*), pressure from without, or the inclosure of fœtal membranes, may have secondarily checked development or have destroyed parts already formed, it is usually difficult to determine; but the symmetrical distribution of the arrested development speaks in favor of the former view.

In cases of *spina bifida* with hernial protrusion, the *local defects in the bony vertebral column and the defective development of the dura mater,* which is usually wanting at the site of the protrusion, are to be regarded as the primary condition. The growth of the sac may be explained as due to congestive and inflammatory transudation, and the residue of inflammatory changes, such as thickenings and membranous adhesions, may often be demonstrated in the pia.

Von Recklinghausen refers the origin of myelocystocele and myelocystomeningocele to a deficient growth in the long axis of the vertebral column, characterized anatomically by shortness of the column, absence of vertebræ or parts of vertebræ, separation of wedge-shaped bony pieces from the bodies of the vertebræ, and by unilateral defects in the arches. The neural canal, then, in the course of normal develop-

ment, becomes too long for the vertebral canal, and in consequence becomes curled or kinked, and there is a tendency to a partial protrusion of the medullary tube at the point of sharpest bending. *Marchand* believes that this hypothesis is not applicable to all cases, and *Arnold* is also of the opinion that the causal relations between arrests of development in the muscle-plates and vertebral anlage on the one hand, and those of the medullary canal on the other, are not constant, but that a variety of harmful influences may give rise to one or more of these anomalies. *Lucksch* emphasizes particulary the effects of pressure as the cause of myeloschisis, but without excluding other causes.

According to *O. Hertwig*, the ordinary spina bifida is an arrest of development depending upon a partially prevented closure of the blastopore ("Urmundspalte").

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§ 134. **Faulty development of the cranium** and the associated **disturbances of cerebral development** lead to those malformations known as *cranioschisis, acrania, hemicrania, microcephalus, anencephalus, exencephalus, micrencephalus, and cephalocele.*

Acrania and **hemicrania** or **cranioschisis** are the results of an agenesia or hypoplasia of the bony and membranous portions of the cranial vault, which arise either as primary disturbances of development or as the result of harmful extrinsic influences upon the cerebral anlage.

Fig. 379.—Anencephalia et acrania. Reduced one-half.

Fig. 380.—Cranioschisis with Exencephalia.

In *acrania* both the bony portion and the skin of the cranial vault (Figs. 379, 381) are wholly wanting, the surface of the base of the skull being covered only with a membranous vascular tissue.

If the defect in the cranial vault is associated with a similar defect in the vertebral arches, there is produced the condition known as **craniorachischisis** (Fig. 376), in which the spinal column is usually shortened and bent, the head in consequence being drawn sharply backward and the face turned upward. Through a marked bulging of the eyes with deficient development of the forehead, these malformations may resemble frogs (*frog fœtus*).

Fig. 381.—Partial agenesia of the bones of the cranium in anencephalia. *a*, Defect; *b*, squamous portion of the occipital bone; *c*, parietal bone; *d*, frontal bone. Reduced one-fifth.

In *hemicrania* the flat bones of the cranial vault have undergone more or less extensive development (Fig. 381, *b*, *c*, *d*) and form a cranial cavity, which is small, in that the flat bones of the vault are elevated but a short distance above the base of the skull. If the bones of the cranium which have undergone an imperfect development yet unite with one another as under normal conditions, there is produced a simple **microcephalus**, which may be present at birth or develop later, as the result of imperfect development of the skull.

Acrania and hemicrania are often associated with **total anencephalus**, the base of the skull being covered only with a membranous, vascular, spongy mass, which is usually composed of vascular connective tissue containing scattered hæmorrhages, and showing no trace of brain tissue or only undeveloped rudiments (*area cerebrovasculosa*).

In other cases the meninges contain, besides cystic cavities and glandlike remnants of the medullary plate, also more or less developed brain-substance, which usually protrudes through the defect in the cranial vault, giving rise to **exencephalus** (Figs. 380, 371). The hernial masses are either inclosed only by a soft membrane corresponding to the inner meninges, or they may be covered also by external skin.

FIG. 382.—Hydrencephalocele occipitalis.

FIG. 383.—Encephalomeningocele nasofrontalis.

With microcephalus there is also **micrencephalus**—that is, an abnormal smallness of the brain. The development of the brain is also usually deficient, or certain portions may be lacking.

If the cranium is in general closed, but presents **partial defects**, portions of the cranial contents may protrude externally in the form of a hernial sac. Such a condition is known as **hernia cerebri** or **cephalocele** (Figs. 382, 383). Defects of ossification, as well as a local weakening of the membranous cranial envelope, are doubtless the primary cause, though adhesions of the meninges with the amnion may also be a cause (St.-Hilaire). The dura mater is wanting over the extracranial portion of the sac (Muscatello).

The size of the protruding sac varies greatly; it may be so small as to be found only after careful examination, or it may be so large as to approach the brain in volume. If only the arachnoid and pia protrude as the result of a collection of fluid in the subarachnoidal space, the hernia is designated a **meningocele**. If at the same time there is a protrusion of brain-substance, it is known as **meningoencephalocele**. A hernia of brain-substance and pia without a collection of fluid is an **encephalocele**; if the protruding brain-substance contains a portion of a ventricle filled with fluid, it is designated a **hydrencephalocele**.

Cerebral hernias occur chiefly in the occipital region (*hernia occipitalis*), close above the foramen magnum (Fig. 382), and at the root of

the nose (*hernia syncipitalis*). In the latter region it may at one time involve chiefly the frontal bone (*hernia nasofrontalis*, Fig. 383), at another time the ethmoid (*hernia nasoethmoidalis*) or the lachrymal bone (*hernia naso-orbitalis*). More rarely hernias occur on the sides of the skull (*hernia lateralis*) or at the base of the skull (*hernia basalis*). The latter may bulge toward the nasopharynx (*hernia sphenopharyngea*), or into the orbit (*hernia spheno-orbitalis*), or into the fossa sphenomaxillaris (*hernia sphenomaxillaris*).

FIG. 384.—Synophthalmos or cyclopia.

In the case of a central hernia the brain may be either normal or more or less malformed. As a result of a marked stunting of development, particularly in the region of the foremost of the three cerebral vesicles, the cerebrum may remain single, while at the same time a *deficient separation of the ocular vesicles takes place* (*cyclencephalia* or *cyclocephalia* of St.-Hilaire). In severe grades of this form of disturbance of development only one eye may be formed, lying in the middle of the forehead, or two eyes united together may be found in one orbital cavity (Fig. 384), so that the malformation may be designated **cyclopia, or synophthalmus,** and as **arrhinencephalus** (Kundrat). The nose is also stunted (Fig. 384) and forms a proboscis-like cutaneous tag attached above the eye, and devoid of bony foundation (*ethmocephalia*).

When the eyes are separate, yet abnormally close together, the nose in general may be normal, though very small at the root (*cebocephalia*).

In the more severe grades of these malformations the ethmoid bone and nasal septum may be wanting, and the upper lip and palate may be cleft in the median line, on one or both sides (Kundrat). In the lighter grades the forehead is merely reduced in size and sharply pointed like a wedge.

FIG. 385.—Cranial cavity of a synophthalmus microstomus opened by a frontal section (seen from behind). *a*, Skin and subcutaneous tissue; *b*, cranium; *c*, dura mater; *d*, tentorium; *e*, arachnoid; *f*, posterior surface of the cerebrum, consisting of a thin-walled sac covered by pia mater; *g*, swollen edge of cerebral sac; *h*, subarachnoidal space behind the cerebral sac; *i*, cavity of the cerebral sac, communicating with the subarachnoidal space through the enlarged transverse fissure; *k*, section through the corpora quadrigemina; *l*, section through the cerebellum; *m*, atlas. Seven-tenths natural size.

In the severe forms of these malformations the cerebrum consists of a sac (Fig. 385, *f*, *i*), occupying more or less of the cranial cavity and filled with a clear fluid; at those points where the sac does not touch the cranial wall the inter-

vening space is filled by fluid distending the subarachnoidal space (*h*). In the less marked forms only individual portions of the brain are undeveloped, those parts chiefly affected being the olfactory lobes and nerves, the corpus callosum, a part of the convolutions, etc. The optic thalami are often blended together. The chiasm and the optic tract may be absent or present. The corpora quadrigemina (*k*), pons, medulla oblongata, and cerebellum (*l*) are usually unaffected.

The spinal cord and brain arise from the medullary canal. In that portion that is to become the brain, the neural canal changes very early into three vesicles. The most anterior of these, the forebrain, throws out from its lateral portions the primary optic vesicles, while the middle portion grows forward and upward and divides into the *telencephalon* or *forebrain*, and the *diencephalon* (*thalamencephalon*) or *tweenbrain*. From the former are developed the cerebral hemispheres, corpora striata, corpus callosum, and the fornix. From the tweenbrain are formed the optic thalami and the floor of the third ventricle. The second vesicle or midbrain forms the corpora quadrigemina, while the third vesicle divides into the isthmus, metencephalon, and myelencephalon, from which there are developed the pons, cerebellum, and medulla oblongata.

The cerebral portion of the medullary canal becomes inclosed by the primitive vertebral plates of the head, which form the membranous primitive skull, the basal portions of which become cartilaginous in the second month of fœtal life. In the third month the basal cartilage and the membranous vault begin to ossify.

According to *G. St.-Hilaire*, *Förster*, and *Panum*, acrania and anencephalus are to be referred to an abnormal accumulation of fluid in the cerebral vesicles, a *hydrocephalus* occurring before the fourth month. *Dareste* and *Perls* oppose this view, and point out that in acrania the base of the skull is usually bulged inward and not pressed outward. They therefore seek the cause of acrania in a pressure exerted upon the cranium from without (*Perls*), due to an abnormal tightness of the cephalic cap of the amnion, which retards the development of the cranium. *Lebedeff* seeks the cause of acrania in an abnormally sharp bending of the body of the embryo, which he thinks occurs when the cephalic end of the embryo grows abnormally in the longitudinal axis, or in case the cephalic covering lags behind in its development.

By the sharp bending the change of the medullary groove into the medullary canal is thought to be hindered, or the canal after its formation is destroyed. From this could be explained the later absence of the brain, as well as of the membranous and osseous cranial covering. The cystic formations in the membranes lying upon the base of the skull are, according to *Lebedeff*, formed from the folds of the medullary plate, which sink into the mesoderm and are then snared off.

Hertwig thinks it possible that chemical substances circulating in the blood or secreted from the wall of the uterus may destroy the anlage of the brain.

According to *K.* and *A. Petrén*, the spinal ganglia in anencephalus are always normally developed; on the other hand, the columns of Clarke, the lateral cerebellar tracts and the bundles of Gowers are either wholly wanting or are imperfectly developed. Likewise the pyramidal tracts are wanting, while the anterior-horn ganglion-cells and the anterior roots are developed. *K.* and *A. Petrén*, therefore, regard the malformation as a system-defect in which the neurones of the second order are not formed; and they incline to the view that the malformation is to be referred to an abnormal anlage of the germ.

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(c) *The Malformations of the Face and Neck.*

§ 135. The development of the face not infrequently suffers disturbances leading to more or less marked **facial malformations,** which may appear alone or in association with malformations of the cranium. If the frontal process and the maxillary processes of the first branchial arch remain in a rudimentary state or are destroyed to a marked extent by pathological processes, there persists at the site of the face an open sinus giving rise to the conditions known as **aprosopia** (*absence of the face*) and **schistoprosopia** (*cleft face*), which may also be associated with a defective development of the nose and eyes.

More frequent than these large defects are smaller clefts involving the lips, alveolar process of the upper jaw, the upper jaw itself, and the hard and soft palates (Fig. 386), which are designated as **cheilo-gnathopalatoschisis** or "**wolf's jaw.**" This malformation gives rise to a communication between the mouth and the nasal cavity (Fig. 386). The hard palate is cleft in the part bordering upon the vomer; the soft palate in the median line. In the alveolar process of the upper jaw the cleft runs between the canine tooth and the outer incisor or between the outer and inner incisors. The malformation may be bilateral or unilateral, and is sometimes primary and inheritable, at other times acquired secondarily, in part as the result of amniotic adhesions (Fig. 371).

Not infrequently the cleft involves only special portions of the regions mentioned, as the upper lip (*harelip, labium leporinum*), or, what is rarer, only the hard or soft palate. The lightest grades of this form of cleft-malformation are represented by a *notch* or *cicatricial line in the lips,* or by a *bifurcation of the uvula.*

Prosoposchisis or **oblique facial cleft** (Fig. 372) is the designation applied to a cleft running obliquely from the mouth to an orbit. It is usually associated with malformations of the brain. According to Morian, three forms may be distinguished. The first is a cleft beginning in the upper lip as a harelip, passing into the nasal cavity, thence around the ala nasi toward the orbit, and may extend even beyond the latter. The second form likewise begins in the region of a harelip, but extends outward from the nose toward the orbit. The third form extends from the corner of the mouth, outward through the cheek toward the canthus of the eye, and divides the superior maxillary process exter-

nally to the canine tooth. A *transverse cleft of the cheek* also occurs, passing from the corner of the mouth toward the temporal region.

Median facial clefts (*nasal cleft*) run in the median line involving the nose, upper jaw, and also the lower jaw, and may extend as far down as the sternum. The tongue may also be cleft. Further, the defect may extend even to the frontal bone and brain.

All of the above-mentioned clefts may be confined to small portions of the regions mentioned, and moreover attain varying depths.

If the development of the inferior maxillary process of the first branchial arch is retarded, the inferior maxilla also is imperfectly developed or wholly wanting, and there arise those malformations known as **brachygnathia** or **agnathia** (Fig. 387). The lower portion of the face

Fig. 386.—Double cheilo-gnathopalatoschisis. (Wolf's jaw.)

Fig. 387.—Agnathia and synotia. (After Guardan.)

appears as if cut away; the ears are sometimes brought so close to each other as to touch (*synotia*). Usually the superior maxillary processes are also imperfectly developed; not infrequently the ear is malformed.

Abnormal largeness of the mouth (*macrostomia*), abnormal smallness (*microstomia*), closure (*atresia oris*), and duplication of the mouth (*distomia*) are all rare.

When the embryonic external branchial clefts or internal branchial pockets fail in part to close, there persist fistulæ opening either externally or internally, or closed cysts. The former condition is known as **fistula colli congenita.** The mouths of the external fistulæ are usually found at the side of the neck, more rarely nearer to the median line or in the median line; those of the internal fistulæ open into the pharynx, trachea, or larynx. Very often the remains of the branchial pockets form only diverticula of the last-named organs. The fistulæ are for the chief part covered with mucous epithelium, sometimes ciliated, arising therefore from the visceral branchial pockets, according to von Kostanecki and von Mielecki usually from the second. In rare cases there is found a complete branchial fistula with both external and internal openings.

The **branchial cysts** arising from the branchial pockets are sometimes lined with mucous epithelium (ciliated epithelium) and contain fluid; hence they are called *hydrocele colli congenita.* At other times they possess an epidermoidal covering and inclose epidermoidal cell-masses, and are therefore classed with the *atheromata* and *dermoid cysts.* Cysts of the neck lying in the median line and reaching to the hyoid bone may develop from remains of the ductus thyreoglossus.

The face and neck are developed in part from a single anlage, and in part from paired anlage. The latter are represented in the branchial or visceral arches growing from the lateral portions of the base of the skull ventrally in the primitive throat-wall. The single anlage, designated the frontal process, is a prolongation downward of the base and vault of the cranium, and is, in fact, nothing more than the anterior end of the skull. Between the individual branchial arches there are at a certain period cleft-like depressions known as the branchial pockets.

The frontal process and the first branchial arch form the boundaries of the great primitive mouth-opening, which has a diamond shape. In the course of development the first branchial arch sends out two processes, the shorter of which applies itself to the under surface of the anterior portion of the head and forms the upper jaw, while from the longer one the lower jaw is developed. The frontal process, which forms the anterior boundary, gives rise to a broad prolongation of the forehead, and then pushes on two lateral processes which are known as the lateral nasal processes. By further differentiation of the central portion of the frontal process proper, the septum narium is formed, which by means of two spurs, the inner nasal processes, produces the borders of the external nasal opening and the nasal furrow. The lateral nasal processes are the lateral portions of the skull, and later develop within themselves the ethmoid labyrinth, the cartilaginous roof, and the sides of the anterior portion of the nares. At a certain stage they form with the superior maxillary process a furrow running from the nasal furrow to the eye, the lachrymal fissure.

In the beginning the mouth is simply a large sinus, but is soon separated into a lower and larger digestive and an upper and smaller respiratory portion. This separation is brought about by the development, from the superior maxillary processes of the first branchial arch, of the palatal plates, which from the eighth week on blend into each other and at the same time unite with the lower border of the nasal septum. The union of the anterior portions of the palatal plates takes place earlier than that of the posterior portions.

Through the union of the contiguous portions of the frontal and nasal processes with the superior maxillary processes the cheek is formed and a continuous superior maxillary border, from which are developed later the lip and the alveolar process of the upper jaw and intermaxillary bones, while the external portion of the nose develops from the frontal process. The intermaxillary bones are developed as independent bones, but unite very early with each other and with the upper jaw.

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(*d*) *Faulty Closure of the Abdominal and Thoracic Cavities, and the Accompanying Malformations.*

§ 136. **Arrests of development in the formation of the ventral body-wall** may take place at different points and exhibit different grades of severity. They occur most frequently in the region of the umbilicus, where the closure of the abdominal cavity takes place latest. In the case of imperfect development of the abdominal wall at this point, so that a more or less extensive area of the abdominal cavity is closed in only by the peritoneum and the sheath of the umbilical cord—that is, the amnion—which are pushed forward by the abdominal organs (Fig. 388), there is produced the condition known as **omphalocele**, or **hernia funiculi umbilicalis**, or **umbilical hernia**. The umbilical cord is attached either to the summit or at one side of the hernial sac, and is more or less shortened.

If the anterior abdominal walls either wholly or in part fail to unite, there arise those conditions which are designated **fissura abdominalis**, or **gastroschisis completa** and **thoracogastroschisis**. These are characterized by the undeveloped abdominal coverings not having been separated from the amnion, but passing into it. The greater part of the abdominal organs lies in a sac formed by the amnion and peritoneum

(*eventration*). The peritoneum, however, may also be wanting, likewise the umbilical cord, and the umbilical vessels may pursue their course to the placenta independently.

A cleft confined to the thorax is called **thoracoschisis.** Should the heart, covered only with pericardium or wholly free, protrude through an opening in the cardiac region, the condition is designated **ectopia cordis.**

When the failure to close is confined to the region of the sternum, the condition is designated **fissura sterni.** This defect may involve either the whole or a part of the sternum, at times affecting the bones, at other times only the skin.

The protrusion of the urinary bladder through a cleft in the abdominal wall is known as **ectopia vesicæ urinariæ.**

Clefts of the abdominal wall are not infrequently associated with clefts of the parts lying behind the wall, not only in the case of large clefts (total), but also in the case of smaller ones (partial). When a cleft of the lower portion of the abdominal wall is associated with a cleft of the urinary bladder, so that the posterior wall of the latter protrudes through the abdominal fissure (Fig. 389, *c*), the condition is known as **fissura,** or **exstrophia,** or **inversio** **æ.** Occasionally the pelvic rethra are also cleft, the latter ed by a groove open anteriorly The exstrophy is then said to y a **fissura genitalis** and **epis-**

lominal fissure or an abdominal ire is combined with a fissure , there is produced a **fissura** **estinalis** or **vesicointestinalis.** The intestinal fissure is situated in the cæcum or beginning of the colon, and the mucous membrane of the cleft intestine protrudes through the opening in the same manner as the posterior wall of the bladder, so that the condition is called **exstrophia** or **inversio intestini.**

If the omphalomesenteric duct does not undergo its normal involution, there remains at the lower end of the small intestine an appendix of intestine called **Meckel's diverticulum,** which arises perpendicularly from the outer margin of the intestine. It has usually the appearance of a glove-finger, and is either free at its end or attached to the umbilical ring, sometimes being dilated at its end. In the case of adhesion to the umbilical ring the intestinal mucosa may appear at the navel in the form of a tumor (*ectopia intestini,*

FIG. 388.—Hernia funiculi umbilicalis. Reduced to one-third.

adenoma umbilicale). In very rare cases a cyst lined with mucous membrane may be formed in the abdominal wall (*omphalomesenteric cyst*).

Congenital fistulæ of the urachus, that is, fistulæ lying within the umbilicus and connecting with the bladder by a fistulous tract, depend upon an incomplete obliteration of the urachus or of the stalk of the allantois. They may be associated either with an open or a closed urethra.

FIG. 300.—Fissura abdominis et vesicæ urinariæ in a girl eighteen days old. *a*, Border of the skin; *b*, peritoneum; *c*, bladder; *d*, small bladder-cavity corresponding to the trigonum; *e*, trough-like urethra; *f*, labia minora.

The development of the body-form from the flat embryonic anlage begins by a snaring-off of the individual germ-layers from the outer embryonal area, and their folding to form two tubes, the body-wall and the alimentary canal.

The infolding of these layers takes place at the cephalic and caudal ends, as well as at the lateral portions of the embryonal anlage, and as the summits of the folds gradually grow together from all directions, those which form the body-wall produce a tube whose cavity finally communicates only at the parietal umbilicus, by means of a peduncle-like prolongation, with the cavity of the extra-embryonic portion of the blastoderm known at this time as the vitelline membrane. While the lateral and ventral walls of the embryo are being thus formed, within the body the intestinal furrow also closes to form a tube, which is in communication at only one point lying within the parietal umbilicus, known as the visceral umbilicus, with the cavity of the umbilical vesicle, by means of a channel known as the omphalomesenteric duct.

Umbilical hernia and clefts of the upper portion of the abdominal wall are frequently combined with craniorachischisis, while exstrophy of the bladder and intestine is often associated with myelocystocele. According to *von Recklinghausen*, the two malformations are to be regarded as coördinated with each other. Further, large abdominal clefts are often associated with lordotic and scoliotic curvatures of the spinal column.

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(c) *Malformations of the External Genitalia and Anus, due to Arrested Development.*

§ 137. Malformations of varying degree of the **external genitals** may be associated with malformations of the abdominal wall, bladder, and the internal genital organs, or may occur independently of these. **Complete absence of the external genitalia** occurs most frequently in connection with other malformations of this region, particularly in the case of sirenomelia, yet the region may in general present also a normal structure (Fig. 392). The internal genitals are usually also malformed.

A **stunted condition of the penis** is not rare, the organ in consequence coming to resemble more or less the clitoris. This condition is usually associated with a **hypospadias**—that is, the urethra opens on the under side of the organ, either beneath the glans, the body or the root of the penis (Fig. 390), or finally even behind the scrotum (*hypo-*

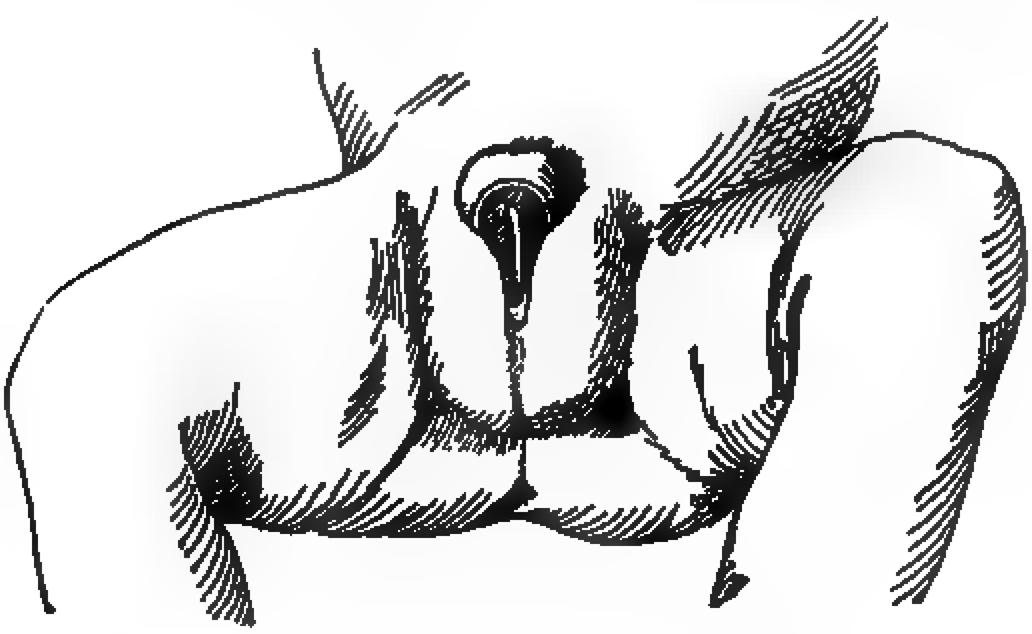

Fig. 390.—Hypospadias with stunting of the penis. Reduced one-fourth.

Fig. 391.—Epispadias. (After Ahlfeld.)

spadias perineoscrotalis). These malformations may exist in penises otherwise normally developed, and depend upon a partial failure of the sexual furrow to close.

Epispadias (Fig. 391) is that condition in which the urethral opening is found upon the dorsum of the penis. It is more rare than hypospadias, and is dependent upon a defective or delayed closure of the pelvis, so that the cloaca, before the closure, becomes divided into an intestinal (anal) and a genital opening (Thiersch). Under certain con-

ditions the penis remains cleft throughout its entire length; at the same time a fissure of the bladder and abdomen may be present.

Hypertrophy of the prepuce is not rare. If the preputial opening is narrowed so that the prepuce cannot be drawn back over the glans the condition is designated a **hypertrophic phimosis. Total absence of the prepuce** is rare; an **abnormal shortness** is more frequent.

Defective development of the scrotum is usually associated with retention of the testicles in the abdominal cavity or in the inguinal canal, and leads to appearances whereby the external genital organs of the male come to resemble those of the female, especially so when the penis is also stunted.

In the female the **clitoris** as well as the **labia majora** and **minora** may show a **stunted development. Epispadias** and **hypospadias** occur also in the female sex, the former coincidently with a fissure of the abdominal and bladder walls (Fig. 389). In hypospadias a portion of the posterior wall of the urethra is lacking, and the urethral opening may be found at a greater or less distance within the vagina.

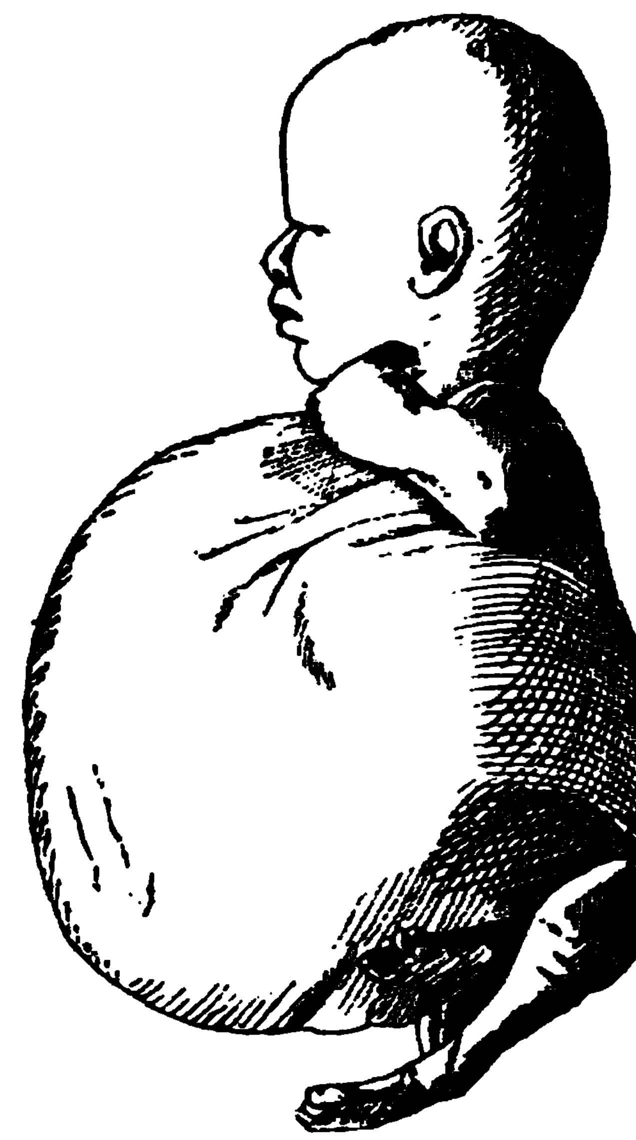

FIG. 392.—Complete absence of the urethra and external genitals, with extreme distention of the body due to an enormous dilatation of the bladder. Compression and stunting of the lower extremities. (In the posterior wall of the bladder rudiments of a female genital apparatus in the form of portions of the tubes and ovaries were found.)

Absence of the urethra occurs in both sexes (Fig. 392). In girls the bladder may open directly into the vagina.

Closure (atresia) of the urethra occurs likewise in both sexes, and results either from a partial defect of the same or from obliteration of the orifice. An accumulation of urine in the bladder may lead to a marked dilatation of the same (Fig. 392).

An **abnomal narrowness of the urethra** may exist in a portion of its course or throughout its entire length. Further, its lumen may be narrowed as the result of a hypertrophic development of the colliculus seminalis.

In rare cases multiple orifices of the urethra have been observed. Further, in men there may be found in the glans penis a blind tube lying beside the urethra.

Atresia ani simplex is a closure of the anus, the intestine being at the same time well developed. It may arise from a failure of the ectoderm to fold in at the anal site, or a cloaca already existing and opening outward may again become closed through subsequent adhesions (Frank). If the rectum does not end immediately above the anal membrane but higher up, there exists in addition to the atresia ani also an **atresia recti,** a malformation which may occur even when the anus is well developed.

When, with absence of the anus, there is also an arrested development of the vaginal wall, which grows downward, between the sinus urogenitalis and intestine, to unite with the perineum, there remains a cloaca

in which the sinus urogenitalis and the end of the bowel unite. In other cases there are found **fistulous communications between the rectum** and the **bladder** or **urethra** (in boys) on the one hand, or between the **rectum** and the **vagina** or **uterus** on the other (*atresia ani vesicalis, urethralis, vaginalis, uterina*).

In rare cases the intestine, in the case of anal atresia, may open outward by means of **external fistulæ** in the perineum, scrotum, or sacrum. Further, external fistulæ below the anus may occur as remains of the post-anal gut.

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(*f*) *Malformations of the Extremities due to Arrested Development.*

§ 138. **Defective development of the extremities** is not rare, and is to be referred in part to a primary defect of the anlage of an extremity, in part to a disturbance in the later development of the limbs or the bones, and in part to constrictions caused by strands of the fœtal membranes or by loops of the umbilical cord. Further, such defective development of the extremities may also follow malformations of the central nervous system. According to the degree and the kind of malformation, the following different forms may be distinguished:

(1) *Amelus.* The extremities are completely absent; in their place are found only warty or stump-like rudiments. The trunk is usually well formed (Fig. 393).

(2) *Peromelus.* Stunting of all the extremities.

(3) *Phocomelus.* The hands and feet are alone developed and are attached directly to the shoulder and pelvis respectively.

(4) *Micromelus* (*microbrachius, micropus*). The extremities are developed, but are abnormally small (Fig. 394).

(5) *Abrachius* and *Apus.* Absence of upper extremities with well-developed lower ones, or *vice versa.*

(6) *Perobrachius* and *Peropus.* Stunting of the upper or lower extremities.

(7) *Monobrachius* or *Monopus.* Absence of one of the upper or lower extremities.

(8) *Sympus, Sirenomelia, Symmelia.* The lower extremities are fused together (Figs. 395, 396), and at the same time turned upon their axes so that their external aspects are in contact. The pelvis is usually

FIG. 393.—Amelus.

FIG. 394.—Micromelus with cretin-like facies.

FIG. 395.—Sympus apus.

FIG. 396.—Sympus dipus.

defective, as are also the external genitalia, the bladder, urethra, and the anus. At the end of the blended extremities feet may be entirely

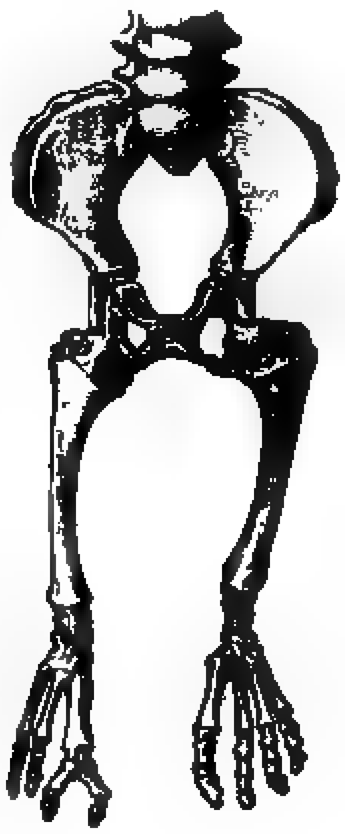

FIG. 397. FIG. 398. FIG. 399.

FIG. 397.—Absence of femur and fibula. Diminution in the number of phalanges. One-half natural size.
FIG. 398.—Perodactylism with syndactylism. Left hand of a new-born child. Seven-eighths natural size.
FIG. 399.—Skiagraph of same hand as in Fig. 398. Seven-eighths natural size.

wanting (*sympus apus*) and only a few toes may be present (Fig. 395); in other cases (Fig. 396) one (*sympus monopus*) or both feet may be present (*sympus dipus*).

FIG. 400. FIG. 401.

FIG. 400.—Malformation of the right hand, perochirus, with blending of the fingers. (After Otto.) *a*, Supernumerary thumb; *b*, thumb proper; *c*, stunted index finger; *d*, middle finger; *e*, ring finger; *f*, little finger.

FIG. 401.—Skeleton of the hand (perochirus) shown in Fig. 400, seen from the dorsal side. (After Otto.) *a*-*f*, as in Fig. 400; *g*, ulna; *h*, radius; *1*, os naviculare; *2*, os lunatum; *3*, os triangulare; *4*, os pisiforme; *5a*, os multangulum majus superfluum; *5b*, os multangulum ordinarium; *6*, os multangulum minus; *7*, os capitatum; *8*, os hamatum.

(9) *Absence of individual bones* may occur in any part of the extremities (Fig. 397).

(10) *Perodactylism—stunting of the fingers or toes*—appears in a great variety of forms, but in general is seen as a defective development (*brachyphalangism*) or complete absence of individual phalanges (Figs. 397, 399, 401, *c*), or as membranous (Fig. 398) or bony (Figs. 399, 401, *d, e*) connections between the fingers (*syndactylism*).

If only the outer fingers or toes are developed while the middle ones are lacking, there arise those formations (Figs. 400, 403) designated as *cleft-hand* and *cleft-foot* (Kümmel). In more extensive malformations

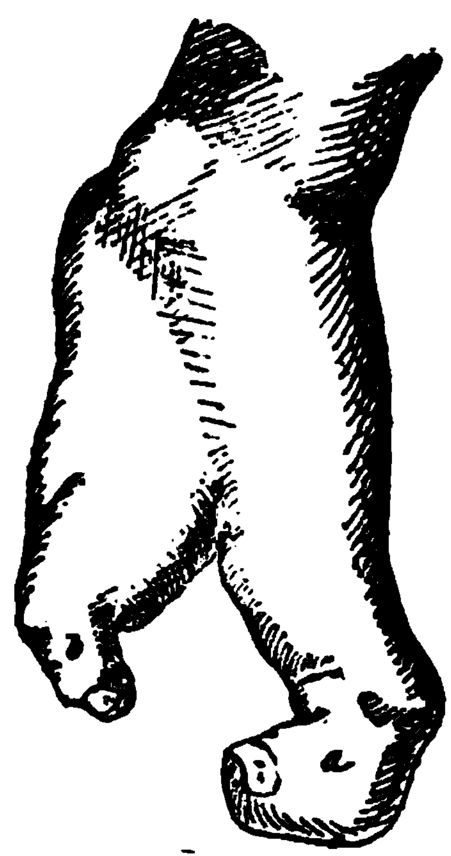

FIG. 402.

FIG. 403.

FIG. 402.—Peropus or cleft-foot. (After Otto.) Right foot. *a*, Great toe; *b*, little toe.

FIG. 403.—Skeleton of the foot in Fig. 402, seen from the dorsal side. *a*, Great toe; *b*, little toe; *c*, rudiment of third toe; *d*, tibia; *e*, fibula; *1*, talus; *2*, calcaneus; *3*, os naviculare; *4*, os cuneiforme majus; *5*, os cuneiforme minus; *6*, os cuneiforme tertium; *7*, os cubiforme.

of the fingers there occur in part also malformations and defects in the region of the tarsal and metatarsal bones (Fig. 403) or carpal and metacarpal bones respectively. These malformations are designated respectively as *peropus* and *perochirus*. Absence of the hand or foot is known as *achirus* or *apus*.

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§ 139. Among the abnormal positions of the extremities **congenital luxations** (slipping of the articular heads from their sockets) are of especial interest. They are most common at the hip-joint, more rare at the elbow-, shoulder- and knee-joints. According to von Ammon, Grawitz, Krönlein, and Holtzmann, the congenital luxations are in part due to *local arrests of development*, but may also be the result of mechanical influences. In the case of the hip-joint the disturbance of development results in a small and imperfect acetabular socket, and the head of the femur is usually more or less imperfectly developed. The small acetabulum lies in the normal position, but the head of the femur is displaced, most often backward (luxatio iliaca). At birth the ligamentum teres is always intact, and the capsule of the joint covers both the head of the femur and the acetabulum. After much use of the leg the ligamentum teres becomes stretched and may tear, the capsule becomes dilated and bag-like, and at the point where it is pressed against the bone may become perforated. A new joint may then be formed through the proliferation of the surrounding tissues.

Abnormal positions of the feet and hands are to be referred partly to disturbances of development and partly to mechanical influences exerted upon the extremities during their growth. The most important is **congenital club-foot (pes equinovarus)**, which, according to Eschricht, is to be referred to an arrest of development, by which the foot is left in the fœtal position, with accompanying abnormal development of the bones and their articular surfaces. The inner border of the foot is

sharply elevated, and the foot at the same time brought into plantar flexion. The collum tali is elongated in an anterior and inferior direction (Hüter, Adams). If the children thus afflicted learn to walk, they tread upon the outer side of the foot, which thereby becomes flattened, while the foot becomes still more sharply turned inward.

Congenital club-foot, though usually to be regarded as a primary disturbance of development of the affected joint, may also under certain conditions be caused by an *abnormal pressure* due to a relatively small uterus (Volkmann). Under these conditions develop also those pathological positions of the foot known as **pes calcaneus** and **pes valgus**, which are characterized partly by strong dorsal flexion and partly by an outward twisting of the foot. Frequently the evidences of the pressure to which the feet have been subjected are seen in an atrophic condition of the skin and portions of the bones.

The position of the hand known as **clubbed-hand** or **talipomanus** is caused by a rudimentary development of the radius, and is usually associated with other malformations.

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2. Abnormal Position of the Internal Organs and of the Extremities.

§ 140. Of the abnormal positions of the internal organs, the most important is the one known as **situs inversus viscerum**—i.e., a *lateral transposition of the internal organs*, so that the position of the thoracic and abdominal organs forms a mirror-image of the normal position. This condition has been observed both in double monsters and in single individuals. It may be restricted to the heart alone, or to the abdominal organs, or more rarely to a part of the latter (*situs irregularis*), but the last is rare. In general, abnormal positions occur especially in the case of the abdominal organs. For example, the kidney is not infrequently

found in an abnormal position (*dystopia renis*), usually abnormally low, so that it approaches the sacral promontory or lies in front of the same. The testis is not rarely retained within the abdominal cavity (*ectopia interna*, or *abdominalis testis*, or *cryptorchismus*), or within the inguinal canal (*ectopia inguinalis*), or at the external ring (*ectopia pubica*), or in the fold between the thigh and scrotum (*ectopia cruroscrotalis*), or in the perineal region (*ectopia perinealis*), or in the fold of the groin (*ectopia cruralis*). *Abnormal positions of the intestines*, particularly of the colon, are not rare.

(*Situs Inversus.*)

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3. Malformations due to Excessive Growth or Multiplications of Organs or Body-parts.

§ 141. The malformation known as **general giant growth** occurs as the result of an excessive growth of the entire body, either during intra-uterine life or later. During extra-uterine life such an abnormal growth may occur that the size of the affected individual may far exceed the maximum normal limits.

Partial giant growth may also take place during intra-uterine life or after birth. The head and portions of the extremities are usually affected. A *unilateral giant growth* is usually restricted to the half of the face or to one extremity, but in very rare cases the hypertrophy may involve all the parts of one side: face, trunk, and extremities. In extra-uterine life trauma sometimes gives the impulse to a pathological excess of growth.

Should the other tissues become so increased in any portion of the body, the extremities, the trunk, or face, that malformations resembling the skin of the pachyderms are produced, the abnormal growth is designated **elephantiasis** (see § 76, Figs. 130, 131). The increase in mass may depend upon a new-formation of connective tissue or adipose tissue or of blood-vessels or of lymphatics. When the thickened regions are sharply circumscribed the formation is regarded as a **tumor** and, according to its structure, is classed with the angiomata, lymphangiomata, or fibromata (see sections treating of these tumors).

Circumscribed hypertrophies of the bones occur in various portions of the skeleton, and are sometimes multiple. The bones of the skull as well as those of the face may be thus affected, and there occur cases in which the hypertrophy of the bone may be so extensive that one or

both of these regions may show marked disfiguration, and there are produced conditions which are known under the general term of *leontiasis ossea* (Fig. 137). Circumscribed hypertrophies of the bones lead to the formation of *osteomata* or *exostoses*, which are often multiple. On the trunk and extremities local growths of bone may lead to the enlargement of single bones as well as to the formation of atypical excrescences known as osteomata and exostoses, which are not infrequently multiple.

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See also § 76.

§ 142. The **occurrence of supernumerary organs, or of a multiplication of parts of the skeleton,** and of **the muscular system,** is relatively frequent. Such phenomena are to be attributed in part to a cleavage or multiple appearance of the given anlage, and in part to a more marked development or persistence of organs which normally remain in a rudimentary state, or undergo retrogression during the period of growth. Further, certain of the conditions included under this head may be regarded as *reversions*.

1. **Duplications of the extremities.** A duplication of an entire extremity without the duplication of the pelvic or shoulder bones has not been observed in man. Duplication of the hands and feet is very rare (Fig. 404), but a number of cases are reported in the literature. The number of fingers may reach nine or ten.

Much more frequent is a **multiplication of the fingers (polydactylism)** on a single hand (or foot respectively), in which condition the supernumerary fingers (or toes) are attached in part at the ulnar or radial side (or tibial and fibular sides respectively), or in part intercalated between the others (Figs. 401, *a*; 405). Often the fingers are duplicated only in part—that is, by the cleavage of the first or the first and second terminal joints (Figs. 406, 407). Those attached at the margin of the hand may be well developed (Fig. 405) or rudimentary. Occasionally they appear as small pedunculated fibrous tumors. In the fully developed supernumerary fingers or toes the phalanges (Fig. 405) may articulate with the metacarpal or metatarsal bones of a neighboring finger or toe, or with their own (supernumerary) carpal or tarsal bones (Fig. 401, *5a*). Polydactylism in certain cases is inherited and is therefore dependent upon

intrinsic causes. In individual cases polydactylism occurs as an inheritable condition and is therefore dependent upon intrinsic causes.

FIG. 404. FIG. 405.

FIG. 404.—Polydactylism with forking of the hand. (After Lancereaux.)

FIG. 405.—Polydactylism in a new-born child. Skeleton. Duplication of the phalanges of the fourth and fifth fingers. Natural size.

FIG. 406. FIG. 407.

FIG. 406.—Polydactylism and syndactylism of the left hand. Reduced one-fifth.

FIG. 407.—Polydactylism and syndactylism of the right foot. Reduced one-fifth.

2. **Supernumerary nipples and breasts (hyperthelia, hypermastia)** are not uncommon malformations in both sexes, and are probably to be regarded as a reversion to polymastic racial ancestors. The supernumerary organs are usually situated on the thorax, along two lines converging from the axillary to the inguinal regions, but in rare cases they may be found elsewhere—in the axilla, on the shoulder, on the abdomen, back or thigh. They are usually small, but in the event of pregnancy may take on functional activity. The number of the nipples may reach as high as ten.

3. The **formation in men of breasts** resembling those of women (**gynæcomastia**) is rarely seen in well-developed men with normal sexual apparatus (see Hermaphrodism, § 143), but it not infrequently happens that the male breast undergoes a moderate enlargement at the time of puberty.

4. **Duplication of the penis** is of very rare occurrence, and may be associated with the formation of two urethræ having independent openings into the bladder, and with two scrota, the two penises being typically developed (Lange).

5. **Supernumerary bones** and **muscles** are of frequent occurrence. *Supernumerary vertebræ* may be found in any part of the spinal column; and at its lower end may in rare cases cause a lengthening of the column, resulting in the formation of a **tail.** According to Virchow, three forms of tails may be distinguished: true tails containing bones; false or imperfect tails which represent an elongation of the vertebral column, but contain neither cartilage nor bones (so-called pig's-tail); and tail-like appendages of skin which consist of different forms of tissue, and in part are to be classed with the teratomata. The true tails are very rare; according to Bartels, they are more often the result of a separation or elongation of the vertebræ than of an increase in their number.

Reduplication of the phalanges of one finger is very rare.

Supernumerary ribs in the neck or lumbar region, as well as a forking of the ribs, are not rare.

Supernumerary teeth also occur.

6. **Duplication** or **cleavage of the anlage** of the **thoracic** and **abdominal organs** occurs most frequently in the case of the spleen, pancreas, adrenals, ureters, pelvis of the kidneys, and lungs, more rarely in case of the ovary, liver, kidney, testicle, and bladder.

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4. True and False Hermaphrodism.

§ 143. The fact that the sexual organs, both the sexual glands and the external genitals, of both sexes, develop from originally similar anlage which contain the beginnings of all the sexual organs of both sexes, makes it *a priori* probable that malformations might result through unequal development of the anlage of the right and left sides, or through a simultaneous development of organs peculiar to both sexes, or finally through a lack of harmonious development of the external and internal genitals.

Those malformations which are to be referred to some one of the factors named, and which are characterized by the fact that the sexual apparatus of a single individual contains parts belonging to both the male and female, are grouped under the designation **hermaphrodismus**. When both sexual glands (testis and ovary) are present the condition is called **hermaphrodismus verus** (*hermaphrodismus glandularis*, Siegenbeek van Heukelom). If the mixing of sexual characteristics consists merely of a combination of male and female genital passages with the external genitalia of the opposite sex, the condition is known as **pseudohermaphrodismus**. The true sex is determined by the nature of the sexual glands.

The body build of hermaphrodites frequently shows a curious mixture of male and female characteristics. For example, the breasts, neck, and shoulders may correspond to the female type, while the development of the beard, face, larynx, and voice may correspond to the male type. In false hermaphrodites the body characteristics do not always correspond to the true nature of the sexual glands; a male may resemble a female, and *vice versa*.

The following **chief types of hermaphrodism** may be distinguished:

1. Hermaphrodismus verus or **androgynes.**—1. *Hermaphrodismus verus bilateralis*, or double-sided hermaphrodism, is characterized by the presence on both sides of both ovary and testis, or the presence on both sides of an organ containing both ovarian and testicular tissue. *Heppner* asserts that in a nine-months-old child, having hermaphroditic external genitals, with vagina, uterus, and tubes, both ovary and testis were found in the broad ligament; epididymis and vas deferens were wanting.

2. *Hermaphrodismus verus unilateralis*, or one-sided hermaphrodism, is that condition in which upon one side there exists but one sexual gland, while on the other both testis and ovary are present. *Salén* has reported a case of a woman of forty-three years of age, who had menstruated since her seventeenth year, in whom there was found upon the right side (castration on account of uterine myoma) a hermaphroditic

FIG. 408.—Hermaphrodismus verus lateralis. (After Obolonsky.) *a*, Urethra; *b*, prostate; *c*, colliculus seminalis; *d*, hymen; *e*, canalis urogenitalis; *f*, bladder; *g*, vagina; *h*, uterus; h_1, left uterine horn; *i*, left tube; i_1, infundibulum of left tube; *k*, left ovary; *l*, ligamentum ovarii; *m*, ligamentum teres sinistrum; *n*, right tube; *o*, right testicle; *p*, epididymis; *q*, right vas deferens; *r*, ligamentum teres dextrum. About one-half natural size. (Specimen in the collection of the Pathological Institute of the German University in Prague.)

gland, the nature of which was confirmed by accurate microscopical examination. The ovarian portion of the gland was typically developed; the epithelium of the seminiferous tubules of the testicular portion consisted of follicular cells and cells of Sertoli, but lacked spermatogonia and seminal cells. *Blacker* and *Lawrence* have also described a case of hermaphroditic gland occurring in a child still-born at eight and a half months. In the hernial sac of an individual twenty years old *Garré* demonstrated the presence of a tube and both sexual glands with parovarium and epididymis (the microscopical examination was made by *Simon*).

3. *Hermaphrodismus verus lateralis* is that condition in which there is an ovary on one side and a testis on the other. It has been many times observed in man (*Rudolphi*, *Stark*, *Berthold*, *Barkow*, *H. Meyers*, *Klebs*, *Messner*, *Kellner*, and others), though in the majority of cases no careful microscopical examination was made, and when carried out, ovarian tissue could not with certainty be demonstrated. Several years ago *Obolonsky* reported a case (a twelve-year-old-girl) from the collection of the German University in Prague, in which the histological examination showed on the right side a testicle (Fig. 408, *o*), and on the left side an ovary (*k*), but it is to be noted that ova were not seen in the latter. The right broad ligament contained a testis (*o*), an epididymis (*p*), a vas deferens (*q*), a rudimentary tube (*n*), a round ligament (*r*); the left broad ligament, on the other hand, contained an ovary (*k*), with an ovarian ligament (*l*), and a well-developed tube (*i*). Moreover, a uterus (*h*), vagina (*g*), and also a prostate (*b*) were present. According to the reported observations, the corresponding

sexual passages may be present or in part wanting. The external genitals are malformed, and combine structures belonging to both sexes.

II. **Hermaphrodismus spurius,** or **pseudohermaphrodismus,** is characterized by a bisexual development of the sexual passages and external sexual organs in association with a unisexual development of the essential sexual gland. The most pronounced cases occur in males, who, in addition to their proper sexual organs, possess a more or less well-developed vagina, uterus, and tubes. It is much more rare to find in females a development of a portion of the Wolffian duct.

In male false hermaphrodites the external genitals are frequently malformed and approach the female type, while in female false hermaphrodites the external genitals resemble those of the male (Fig. 409).

The resemblance of the male external genitals to those of the female is brought about by a stunting of the penis and a total or partial failure of the sexual furrow in the penis to close (hypospadias), so that the two halves of the scrotum are separated, leaving a depression beneath the root of the penis, which represents the remains of the sinus urogenitalis. The scrotal halves come, therefore, to resemble the labia majora, particularly in the case of non-descent of the testicles. The external genitals of the female approach in appearance those of the male through the development of the clitoris into a sort of penis (Fig. 409, *a*), while the vaginal opening is narrowed or closed through the union of the labia. The vagina and urethra have a common opening, or open separately beneath the penis-like clitoris.

The atypical development of the external genitals may or may not be associated with malformations of the sexual passages, and is, therefore, not dependent upon malformations in other portions of the sexual apparatus.

FIG. 409.—External genitals of a female false hermaphrodite, with stenosis of the vaginal orifice. *a*, Penis-like clitoris; *b*, labia majora. Reduced one-ninth.

1. *Pseudohermaphrodismus masculinus* occurs in three varieties:

First, *pseudohermaphrodismus masculinus internus*, in which condition the external genitals are of the male type, and the prostate is developed, but is usually pierced at the colliculus seminalis by a canal opening into the urethra, the former being continued above into a rudimentary or more or less well-developed vagina, often also into a more or less well-formed uterus, and even tubes. The male organs may be well developed or more or less malformed.

Second, *pseudohermaphrodismus masculinus completus*, or *externus et internus*, in which form the vagina, uterus, and tubes are present in a state of rudimentary or more or less complete development, while the external genitals resemble more or less completely the female type. The penis presents the condition of hypospadias and resembles the clitoris; beneath it lies a furrow at whose posterior end there is usually an orifice leading into a short vestibule which divides at once into a urethra and a vagina. Sometimes the vagina and vestibule are separate. In rare cases the external genitals appear normal, but the penis contains a double canal, the upper one representing the urethra, the other the sexual passage. In the case of a more marked development of the ducts of Müller the vasa deferentia are frequently defective, and the seminal vesicles are sometimes wanting.

Third, *pseudohermaphrodismus masculinus externus*, in which only the external genitals depart from the male type, and resemble more or less closely the female. As in these cases the bodily habitus often simulates that of the female, the true sex of the individual may easily be mistaken.

2. *Pseudohermaphrodismus femininus* also occurs in three similar varieties, but is much more rare.

In *pseudohermaphrodismus femininus internus* rudiments of the Wolffian ducts, lying in the broad ligament or in the uterovaginal wall, and sometimes extending to the clitoris, are found in association with well-developed external genitals.

Pseudohermaphrodismus femininus externus is characterized by external genitalia resembling those of the male (Fig. 409).

Pseudohermaphrodismus femininus externus et internus, in which the external genitals resemble those of the male and there is a persistence of parts of the Wolffian ducts, is very rare. Of the internal male genitalia, there was found in one case a prostate, and in another case a prostate pierced by the vagina, an ejaculatory duct, and a sac resembling a seminal vesicle, which opened into the vagina.

The **internal sexual organs** develop from the same undifferentiated anlage in both males and females. These anlage consist of a sexual gland lying on the medial anterior side of the *Wolffian body*, and a *sexual passage* known as the *duct of Müller*. The latter develops beside the *Wolffian duct*, and, like it, empties into the lower end of the bladder or into the sinus urogenitalis.

In the *male* the *duct of Müller* disappears, only slight traces in the form of the uterus masculinus or vesicula prostatica remaining; the primitive sexual gland unites with a small part of the *Wolffian body*, which becomes the head of the epididymis, another small portion forming the vasa aberrantia testis (organ of *Giraldes*), the remainder disappears, while the *Wolffian* duct becomes the vas deferens and vesicula seminalis.

In the *female* the *Wolffian body* and its *duct* disappear, leaving only a trace in the form of the gland-tubules known as the parovarium, but remains of the duct are not infrequently found preserved in the uterine wall. From the *ducts of Müller*, which in part coalesce at their lower ends, develop the vagina, uterus, and tubes. The extreme upper end of the duct of *Müller* not infrequently persists in the form of a little pedicled sac attached to the abdominal end of the tube, the hydatid of *Morgagni*.

The anlage of the *sexual glands* appear in the fifth week. In mammalia (probably also in man) they develop through a localized thickening of the peritoneal epithelium, which becomes the germinal epithelium (*Waldeyer*), while at the same time the mesoderm also proliferates. Whether the seminal tubules arise from peritoneal epithelium (*Bornhaupt Egli*), or whether they are derived from an ingrowth of the Wolffian body into the testis-anlage (*Waldeyer*), is still an undecided question (*Kölliker*). The ova arise from germinal epithelium. The environing cells of the Graafian follicle are regarded by *Waldeyer* as also derived from the germinal epithelium; while *Kölliker* believes that they probably arise from the Wolffian body.

The significance of the *pedunculated* and *non-pedunculated hydatids*, found in varying numbers near the globus major of the epididymis, is not yet determined (*Kölliker*). The non-pedunculated cyst known as the hydatid of Morgagni is regarded by *Waldeyer* as a remnant of the duct of *Müller*. According to *Roth*, it may also stand in a close relation to the *Wolffian* body, inasmuch as there is occasionally found a vas aberrans of the epididymis communicating with it.

In the development of the vagina and uterus the ducts of *Müller* and the *Wolffian* ducts unite at their lower portion to form a rounded quadrangular cord, the genital cord. At the end of the second month the ducts of *Müller* blend to form a single canal, which then develops into the vagina and uterus. This union takes place first near the middle of the genital cord. The Wolffian ducts play no rôle, though remains of these are found at birth in the broad ligament (*Kölliker*) and in the wall of the uterus (*Beigel*). According to observations of *Riedel*, remains of the Wolffian duct are found in about a third of adult females, in the form of a tube lined by cylindrical epithelium surrounded by muscle, or as a muscle-bundle without epithelium, lying anteriorly and to the side of the uterus and vagina.

The **external genitals** begin to develop, even before the cloaca has separated into the intestinal and genito-urinary orifices, by the formation, in the sixth week, of a median genital tubercle in front of the cloaca, and further, of two lateral folds, the genital folds. Toward the end of the second month the tubercle becomes more prominent, and shows on its lower surface a furrow, the genital furrow. In the third month the cloaca becomes divided to form the anal and genito-urinary openings. In the male embryo the genital tubercle becomes the penis, the glans being recognizable as early as the third month. In the fourth month the furrow closes to form a tube; at the same time the two genital folds unite to form the scrotum.

The prepuce is formed in the fourth month. The prostate arises in the third month as a thickening of the tissues at the junction of the urethra and the genital cord. The glands of the prostate develop in the fourth month from the epithelium of the canal and grow out into the surrounding connective tissue.

In the female embryo the closure of the genital furrow and the genital folds does not take place, so that the sinus urogenitalis remains short. The genital eminence becomes the clitoris, the folds become the labia majora, and the edges of the genital furrow the labia minora.

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5. Double Monsters.

(a) *Classification of Double Monsters.*

§ 144. **Twin-formations** lying within a single chorion may be divided into two large groups: *twins completely separated from one another*, and *twins united by some portion of their bodies.*

Of the **twins completely separated from one another** there may be distinguished two types; one in which *both twins are fully developed*, and one in which *one twin is stunted.*

Twins joined together by portions of their bodies may likewise be also divided into two groups: *twins showing uniform development* and *twins*

showing an unequal development. To the latter belongs an especial group of greatly stunted parasitic forms that may be classed as teratomata.

According to the situation of the duplicated portions of the body, there may be distinuished (Foerster):

1. Monstra duplicia katadidyma or duplicitas anterior.
2. Monstra duplicia anadidyma or duplicitas posterior.
3. Monstra duplicia anakatadidyma or duplicitas parallela.

In general, these may also be conveniently divided into three classes (Taruffi):

1. Twins united chiefly by the epigastrium and thorax.
2. Twins united chiefly by the heads.
3. Twins united chiefly by the pelves.

FIG. 410.

FIG. 411.

FIG. 410.—Acardius acephalus, showing a rudimentary development of the lower extremities (acardius amorphus).

FIG. 411.—Acardius pseudoacormus. (After Barkow.) *a*, Head; *b*, rudiment of the left upper extremity; *c*, rudimentary intestine; *d*, artery; *e*, vein.

Ahlfeld divides the double monsters into two chief groups, those with *complete* and *those with partial doubling of the axial structures.*

In very rare instances **triple monsters** occur.

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See also § 131.

(*b*) *The Chief Forms of Double Monsters.*

§ 145. **Twins separated from each other** and lying within a *single chorion* are designated **homologous twins.** They are always of the same

sex, have usually a common placenta, and resemble each other very closely. If from any cause one of the twins should die after its body has been developed, it may be pressed flat by the continued growth of its fellow, giving rise to the condition known as **fœtus papyraceus.**

When twins possess a common placenta within which the blood-vessels have abundant anastomoses, the heart of the stronger fœtus may control the circulation and thereby cause changes in the direction of the blood-stream in the weaker twin. As a result of this the latter suffers severe disturbances of development, and becomes changed into an **acardius,** a *monster without a heart*, either developing no heart at all or only a rudimentary one. In the majority of such cases the *head also fails to develop* (*acardius acephalus*) or remains *rudimentary* (*acardius paracephalus*), and likewise there is usually no development, or only a rudimentary one, of the upper extremities, thorax walls, lungs, and liver, while the abdomen, pelvis, and lower extremities are more or less perfectly formed (Fig. 410). According to the development of the extremities the following varieties may be distinguished: *acardius paracepalus* (*or acephalus*) *sympus, monopus, dipus, monobrachius, dibrachius.*

In rarer cases there is no recognizable development of any part of the body, and there is formed an *acardius amorphus*, consisting of a shapeless mass covered with skin, usually without any indications of extremities, and possessing internally only rudiments of organs.

Of very rare occurrence is the formation known as an *acardius pseudoacormus* (Fig. 411)—that is, a monster in which the head (*a*) only is developed, while the other parts of the body are represented only by small rudiments (*b*, *c*).

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See also § 147.

§ 146. **Twins equally developed and united to each other** occur in the following principal types:

1. **Duplicitas anterior** (*monstra duplicia katadidyma*). Anterior duplication with union of posterior portions of the body.

Pygopagus (Fig. 412). Union of the twins in the region of the coccyx or of the sacrum. According as the union is more or less extensive, the sacrum, coccyx, lower end of the medullary canal, anus, lower end of the bowel, and the sexual apparatus are either doubled or are in part single.

Ischiopagus (Fig. 413). Union of the twins in the pelvis, which thereby forms a wide ring, the two sacra being placed opposite each other. The anus, lower end of the bowel, and the sexual organs may be single or double, and the number of the lower extremities two to four.

Dicephalus (Fig. 414) and **diprosopus** (Fig. 415). The duplication is limited to the upper part of the trunk and head, or only to the neck and head, or the head alone, or, finally, only to portions of the head. As the external blending increases in extent, there occurs also a blending

FIG. 412. FIG. 413.

FIG. 412.—Pygopagus. (After Marchand.) *A*, *B*, The two twins; *a*, *b*, separated umbilical cords; *c*, blended umbilical cords; *d*, common placenta. There is a single coccyx and sacrum (from the second vertebra downward), and the lower end of the medullary canal is single. The two intestinal canals terminate in one anal opening. Vestibule of vagina single, the remaining portions of the sexual organs double.

FIG. 413.—Ischiopagus. (After Levy.)

of the internal organs, the intestine, liver, lungs, heart, spinal cord, brain, etc. According to the number of the lower and upper extremities there may be distinguished *dicephalus tetrapus*, *dipus*, *tetrabrachius*, *tribrachius dibrachius* (Fig. 414). When the heads have blended there may be distinguished *diprosopus tetrophthalmus*, *triophthalmus*, *diophthalmus*, *tetrotus*, *triotus*, *diotus*, *distomus*, *monostomus*, *tribrachius and dibrachius* (Fig. 415).

The mildest grades of duplicitas anterior are represented by the rare cases of *duplication of the jaw*, *mouth*, or *nose*.

2. **Duplicitas posterior** (*monstra duplicia anadidyma*). Union of the twins at the head and thence farther downward with duplication of the posterior parts of the body.

Craniopagus (Fig. 416). Union of the twins in the cranial region. According to the site of union there may be distinguished *craniopagus parietalis*, *frontalis*, *occipitalis*. When the union is more extensive portions of the brain are also single.

Cephalothoracopagus or **syncephalus** (Fig. 417). Blending of the

twins in the region of the forehead and face, and in part also of the abdomen. In the region of the united heads there is an anterior and a posterior face (*janus, janiceps*). The two faces may be equally (*janus symmetros*) or unequally developed (*janus asymmetros*), one face being well developed, the other imperfectly. The internal organs present different degrees of blending and union into single organs.

Dipygus. The duplication is limited to the lower half of the body and the lower extremities, while the upper parts are either wholly single or only partly cleft. The duplication of the spinal cord may begin at different heights. According to the number of extremities different

FIG. 414.—Dicephalus dibrachius dipus.

FIG. 415.—Diprosopus distomus tetrophthalmus diotus dibrachius.

forms may be distinguished. The mildest grades of duplication are confined to the lower end of the spinal column, the anus, and the external genitals.

3. **Duplicitas parallela** (*monstra duplicia anakatadidyma*). Duplication of the anterior and posterior ends of the body with parallel positions of the trunk.

Thoracopagus (Fig. 418). Union of the twins by the thorax. According to the site and extent of the union, as well as the number of extremities present, there may be distinguished different forms, particularly the following: *xiphopagus* (union at the xiphoid process), *sternopagus* (union at the sternum), *thoracopagus tetrabrachius, tribrachius, dibrachius, tetrapus, tripus,* and *dipus*. When portions of the faces have blended

there results a *prosopothoracopagus*. Blending and union of the internal organs into single organs vary with the degree of external blending. The heart may be double or single, in the latter case malformed. Thoracopagus is relatively frequent.

Rachipagus. Blending of the twins in the region of the spinal column is very rare.

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FIG. 416. FIG. 417.

FIG. 416.—Craniopagus parietalis.

FIG. 417.—Cephalothoracopagus or syncephalus, with janus head. Both anterior and posterior faces are malformed, and possess but one eye, while the nose is represented by a proboscis-like organ situated above the eye.

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See also §§ 131 and 147.

§ 147. **Twins joined together but unequally developed** may occur in any of the double forms described in § 146. If the development of one of the twins remains rudimentary and if its heart does not develop, its nourishment can come only through its well-developed fellow. The better developed of the two is then known as the **autosite,** the other as the **parasite.** If the parasite is of only very rudimentary development, it may be classed with the **bigerminal teratomata** (cf. §§ 127 and 128).

FIG. 418.—Thoracopagus tribrachius tripus. The hand of the third arm, common to both halves, possesses two dorsal surfaces, and the laterally distorted fingers possess nails on both sides. The common third foot has eight toes.

At the *posterior ends of the body* there may occur a rudimentary double monstrosity in the form of an *increase in the number of the extremities, a polymelos* (Figs. 419, 420). In so far as the lower extremities are concerned such a malformation may be classed as an ischiopagus or a dipygus. The supernumerary extremities may be one or two in number, and more or less well developed. Further, there not infrequently occur *coccygeal teratomata* in which the presence of rudimentary extremities (Fig. 421, *a*, *b*, *c*) or of various body elements leaves no doubt that the tumor-like formation covered by the skin of the autosite is to be regarded

as a double monster, a *rudimentary pygopagus,* or else as *dipygus parasiticus.* Such a parasite is designated as an *epipygus.*

Supernumerary extremities (Fig. 422) may also be found upon the

FIG. 419.—Polymelos. (After Lancereaux.)

FIG. 420.—Polymelos. (After Liesching.)

FIG. 421.

FIG. 422.

FIG. 421.—Bigerminal teratoma of the coccygeal region (pygopagus parasiticus). *a, b, c,* Extremities lying in a sac formed by the skin of the autosite.

FIG. 422.—Thoracopagus parasiticus (thoracomelus). Three legs spring from the pelvis; one of them has a double foot. Two upper extremities project from the anterior chest-wall.

trunk, or *there may occur a headless trunk with extremities* (Fig. 423), or a *rudimentary thorax without extremities*, or, finally, *teratomata* which may be interpreted as *thoracopagus parasiticus* (*omphalopagus*) and as *dipygus parasiticus*. The malformation is also often called *epigastrius*.

The inclusion of such teratomata beneath the skin of the abdomen or thorax, or within the abdominal or thoracic cavities of the autosite, gives rise to the condition known as *inclusio fœtalis subcutanea*, or *abdominalis*, or *mediastinalis*. The abdominal inclusion is also designated *engastrius*.

FIG. 423.

FIG. 424.

FIG. 423.—Thoracopagus parasiticus. (After Schenk von Gräfenberg.) Parasite attached to chest of autosite.

FIG. 424.—Epignathus. (After Lancereaux.)

In the *region of the head* rudimentary twin-formations appear most often in the mouth cavity, forming usually an amorphous mass, firmly attached to the base of the skull, and consisting of skin, connective tissue, cartilage, bone, brain-tissue, teeth, intestinal elements and muscle, and rarely developed extremities. Such malformations are included under the designation of *epignathus* (Fig. 424).

On other parts of the head (*prosopopagus parasiticus*) rudimentary twin formations or bigerminal teratomata are very rare (cf. §§ 127, 128); but they occur also in the cranial cavity (*encranius*) and in the neck (*hygroma colli*).

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See also §§ 127, 128, 131, 144, and 146.

CHAPTER X.

The Pathogenic Fission-fungi and the Diseases Caused by Them.

I. General Considerations Regarding the Schizomycetes or Fission-fungi.

1. General Morphology and Biology of the Fission-fungi.

§ 148. The **Schizomycetes** or **fission-fungi**, often also designated collectively as **bacteria**, belong to the *protophytes*—that is, to the smallest simplest forms of plant-life. Many of them are so small that they stand upon the very border-line of invisibility even with the use of the highest-power objectives and eye-pieces. When occurring in animal tissues, it is often very difficult to distinguish them from the products of cell-disintegration; and often this can be accomplished only through the employment of specific reagents or staining-methods, and occasionally only through culture experiments.

The *Schizomycetes* throughout are *non-chlorophyllaceous, unicellular organisms,* but as a result of their growth and multiplication they often form colonies made up of numerous cells.

The form and character of the single cells, as well as their manner of growth, division, and multiplication, vary greatly, and at present these differences are used as a basis for the classification of bacteria. In the first class are placed the **Cocci**, often designated as *Micrococci* or as *Sphærobacteria* (Cohn), that form of bacteria which constantly occurs in the form of *spherical* or *oval cells.* According to the grouping of the cells during their division, there may be distinguished six forms of cocci: *double-cocci* or *Diplococci, chain-cocci* or *Streptococci, clustered cocci* or *Staphylococci, tablet-cocci* or *Merismopedia, packet-shaped cocci* or *Sarcinæ,* and *tube-cocci* or *Ascococci.*

The second class constitutes the **Bacilli** (rod-shaped bacteria) which formerly were divided by Cohn into *Microbacteria* and *Desmobacteria,* according to the length of the rods. These may also be designated as *short rods* and *long rods.* In association with the designation *bacillus* many authors use the term *Clostridium,* particularly for bacilli which during spore-formation assume spindle or club shapes. Long threads are often also called *Leptothrix.*

To the third class belong the **Spirilla** (screw-shaped bacteria). Screw-shaped forms with short, wide turns are known as *Spirilla,* those with drawn-out turns as *Vibrios,* those with a long, closely wound screw as *Spirochætes.* According to their length the spirilla may also be divided into *short screws* and *long screws.*

All of the bacteria thus far referred to occur either in one single form or in a very limited cycle of forms of growth, and they may therefore be grouped together as **monomorphous** or **oligomorphous bacteria.** Cohn,

to whom we are indebted for the fundamental investigations regarding bacteria, united under the term bacteria only the oligomorphic forms.

Many writers, however, classify also as bacteria those organisms which during their development pass through a whole series of forms: spherical cells, as well as rods and simple and branching threads. These may be collected into a second group—the **polymorphous bacteria**—to which belong in particular the fungi known as *Streptothrix*, *Cladothrix*, *Beggiatoa*, *Crenothrix*, and *Actinomyces*. Other authors (Lehmann, Neumann, Levy, Lubarsch) class these forms with the *Hyphomycetes* or regard them as transition forms between the latter and the *Schizomycetes*. Petruschki collects them under the family term of *hair-fungus* or *Trichomycetes*, and classes them with the *Hyphomycetes*.

All of the Schizomycetes consist of a plasmatic **cell-contents** and a **cell-membrane**, both of which, according to Nencki, consist essentially of an albuminoid body, **mycoprotein**, which varies with the species. Many bacilli contain fat within their cell-bodies, at times so abundantly that it may be demonstrated by staining with Sudan III. Some of these bacteria (tubercle-bacillus, lepra-bacillus, and actinomyces) show the presence of fat both when growing in living tissues and when cultivated upon artificial media; others (staphylococcus aureus, anthrax-bacillus, bacillus of glanders) show the presence of fat only when grown upon certain media (Sata). In many forms of bacteria the membrane under certain conditions may swell and appear as a hyaline *capsule* surrounding the bacterial cell.

In all forms of bacteria, with the exception of the cocci, there have been observed swarming **movements** which are brought about by means of fine thread-like **flagella** attached singly at the ends or scattered over the entire bacterial cell. In addition there also occur slow oscillatory or gliding and creeping movements which are dependent upon the contractile and flexible qualities of the plasma. Both forms of motion occur only under certain conditions of nutrition and growth, and only in certain species.

Multiplication of bacteria takes place through a **transverse division** of cells which have previously become elongated. In some forms division can also take place in two or even three dimensions. After division the cells separate immediately or remain for a time attached to each other. When the cells remain attached after dividing transversely, **threads** are formed (*Streptococcus*, *Leptothrix*); after dividing both transversely and longitudinally, **flat, tablet-like colonies** (*Merismopedia*); after dividing in all three dimensions, **colonies resembling a solid body** (*Sarcina*) are produced. Long threads may become segmented into shorter pieces.

According to the investigations of Buchner, Longard, and Riedlin, the period of reproduction—that is, the time from one cell-division to the next—is, in the case of the cholera-spirillum under favorable conditions of nutrition, about fifteen to forty minutes.

If resting bacterial cells, as the result of a constantly progressing reproduction or through the accumulation of neighboring cells, heap themselves anywhere in great masses, there are often formed jelly-like colonies, which are called **zoöglœa**. The jelly-like substance is formed from the membranes of the bacteria and, according to Nencki, consists of mycoprotein. The jelly masses may assume the most varied form, and occasionally reach a large size, so that the clumps, or lobulated masses, or strands may attain a diameter of one to three or more centimetres.

Under certain conditions many of the bacteria form **spores**. These are cells which are distinguished by the fact that they remain alive under conditions in which the ordinary forms of vegetation die; and, when brought into fresh nutrient solutions, are able to produce a new generation. *Spore-formation* is most frequently *endogenous*—that is, the spore arises inside the cells (particularly in bacilli), and is developed out of the cell-protoplasm, in which there appears a small granule which grows into an oblong or round, highly refractive, sharply-contoured body always remaining smaller than the mother-cell. After the death of the latter the spore is set free. *Arthrogenous spore-formation*, as observed in micrococci, is said to occur through the direct assumption of spore-qualities by individual members of a colony or of a series of generations, which at the same time remain externally unaltered or take on other morphological peculiarities.

In old cultures bacteria nearly always show **degeneration-forms**, which are swollen and distorted, and stain poorly and irregularly.

As non-chlorophyllaceous plants, the schizomycetes are restricted in their **nutrition** entirely to ready-formed **organic substances** which are soluble in water, and which are also supplied to them in an abundance of **water**. In addition they need also **various mineral substances**, especially sulphur, phosphorus, potassium or rubidium, or cæsium and calcium (or magnesium, barium, or strontium). Changes in the conditions of nutrition may modify the form and dimension of bacteria and also change their vital properties.

Some of the fission-fungi are either chiefly or wholly restricted for their food-supply to dead organisms or to solutions of organic matter, and are, therefore, classed as **saprophytes**; others are able to take their nutrition also from living animals or plants, and live as **parasites.**

If bacteria get into water which contains no food-material, many of them die in time. The spores survive the longest.

Free **oxygen** is necessary for the development of many bacteria; others can dispense with it as long as they are under favorable conditions of nutrition in other respects; others develop only in the absence of oxygen. The first are designated *obligate aërobes,* the second *facultative anaërobes,* the third *obligate anaërobes.*

The pathogenic bacteria are, according to Liborius, facultative or obligate anaërobes.

Carbon dioxide has no influence upon the development of many bacteria, as, for example, upon the typhoid-bacillus and Friedländer's pneumobacillus. Upon others, on the contrary, it has an inhibitory action, as, for example, upon *Bacillus indicus, Proteus vulgaris, Bacillus phosphorescens,* the bacilli of anthrax and cholera, the pus-cocci, and others (C. Fränkel). The bacilli of anthrax, Asiatic cholera, and of rabbit septicæmia die out in a few hours in artificial Seltzer water, but anthrax-spores remain alive in it indefinitely (Hochstetter).

Intense **light** has an injurious or destructive influence upon the development of many forms of bacteria, and it is therefore possible to disinfect by means of strong light water which is infected (Buchner). The virulence of the bacillus of anthrax may be lessened by exposure to sunlight (Arnold, Gaillard). When exposed to the direct rays of the sun anthrax bacilli die in twenty-four to thirty hours, the spores survive as long as six to eight weeks (Arloing, Duclaux). According to Geisler the green, violet, and ultra-violet rays are particularly active. According to Rieder bacteria may be destroyed by the Roentgen-rays.

The temperature of the surrounding medium acts in general upon the bacteria in such a way that when it falls the life-processes of the organisms become weaker and slower, and finally cease entirely, whereas with an elevation of the temperature they rise to a certain maximum, and at a slight increase above this suddenly cease; still higher temperatures kill the fungi. The maximum of permissible temperature lies at a different height for different fungi, and is in part dependent also upon the character of the nutrient substance. There are forms of bacteria which grow well at a temperature of 55° C. or higher.

A low temperature checks development in all varieties; they fall into a state of immobility, but do not die even at great degrees of cold. The immobility due to cold occurs at different temperatures with different varieties. The most favorable temperature for development lies between 30° and 40° C. for the anthrax bacillus; at temperatures above 44° and below 15° C. its development ceases. Many bacilli form spores only at high temperatures.

Boiling water and *steam* at 100° C. kill all bacteria and bacterial spores if allowed to act for some time. In dry air bacteria and their spores withstand higher temperatures, so that a temperature of 140° C. for three hours is necessary to kill the latter. Many bacteria are killed at a temperature of 60° to 70° C., provided it is kept up for a very long time.

Anthrax-spores die in boiling water in two hours, in confined steam in ten minutes. The action of steam at 105° C. for ten minutes kills all spores. *Live steam* kills all spores in ten to fifteen minutes, and penetrates very well into the objects to be disinfected (Koch, Gaffky, Löffler).

If fission-fungi find themselves in a suitable medium, their multiplication can still be brought to a standstill, since the fluid may contain **substances which hinder the growth of the bacteria** or **even kill them.** This effect is produced by many substances (sublimate, lysol, carbolic acid, iodine, formaldehyde, etc.)—even in comparatively great dilution. Other substances act injuriously upon the bacteria only when in stronger concentration. The point at which the multiplication is hindered is always reached at a much greater dilution than that at which the bacteria are killed. Spores are much more resistant than the vegetative forms.

The growth and multiplication of bacteria also cease in the case of **insufficient amount of water.** The fact that fruits preserved in sugar do not ferment and that salted and dried meats do not putrefy depends upon this fact. Food-stuffs can also be preserved through the removal of water and by the addition of substances which are dissolved in the tissue-fluids and in this way increase the proportion of the same in solid contents. The limit at which the fission-fungi and yeast-fungi cease to develop is reached at a much higher degree of humidity than for the moulds.

If a nutrient fluid contains other lower fungi besides the bacteria there often takes place **a competition between the different micro-organisms**; and fission-fungi, yeasts, and moulds may crowd one another out. Likewise a reciprocal **crowding between the bacteria themselves** may occur. For example, cocci may be crowded out and destroyed by bacilli, or one form of bacillus by another. This would happen when either the composition or the temperature of the nutrient medium is more favorable to one form than to the other; or also when one form of bacteria produces products which act injuriously upon the other, or when one form grows more rapidly than the other, and thereby deprives its competitor of the necessary food-supply.

According to investigations by Pasteur, Emmerich, Bouchard, Woodhead, Blagovestchensky, and others, the antagonism between many forms of bacteria is shown also in inoculation experiments on animals. By simultaneous inoculation with different bacteria the development of a pathogenic bacterium in the body of a susceptible animal may be hindered. For example, the development of anthrax bacilli may be hindered by simultaneous inoculation with erysipelas-cocci (Emmerich) or with the *Bacillus pyocyaneus* (Bouchard).

The question as to whether the bacterial cell contains a **nucleus** has been a subject of much discussion. *A. Fischer* denies it, while *Bütschli*, *Schottelius*, *Ziemann*, *Zettnow*, *Nakanishi*, and *Feinberg* are inclined to favor the affirmative view. According to *Zettnow*, the bacterial cell contains chromatin or nuclear substance mixed with the entoplasm; while the covering of the cell, or ectoplasm, does not contain chromatin. According to the investigations of *Ziemann*, *Zettnow*, and *Feinberg*, it is possible through staining with a mixture of methylene-blue and eosin (*Romanowski*-stain) to demonstrate within the majority of bacteria a "nuclear substance" or "chromatin" (*Ziemann*, *Zettnow*) or a "nucleus" (*Feinberg*)—that is, there may be demonstrated within the bacteria structures of varying size which stain red like the nuclei of malarial plasmodia (*Romanowski*) or of other protozoa or of tissue-cells, while the cell-plasma takes a blue stain. According to *Nakanishi*, circumscribed nuclei are found in young forms.

The *Romanowski*-stain is a mixture of methylene-blue and eosin, whereby a red dye contained in methylene-blue (*Rosin*, *Berl. klin. Wochen.*, 1899; *Nocht*, *Cbl. f. Bakt.*, 1899) is precipitated. *Zettnow's* formula is as follows: 50 c.c. of a one-per-cent solution of a *Höchst* methylene-blue is treated with 3–4 c.c. of a five-per-cent solution of soda. To 2 c.c. of this there is added drop by drop while shaking 1 c.c. of a one-per-cent solution of *Höchst* eosin BA. Stain five minutes on cover-glass and examine in water.

According to *Nägeli*, *Zopf*, and others, many fission-fungi possess a membrane of cellulose or of a carbohydrate closely related to cellulose. Certain bacteria (*red sulphur bacteria*) combine within their cell-substance coloring-matter; others (*Bacillus amylobacter*, *Spirillum amyloferum*) give at certain stages of their development the starch reaction with iodin.

Babes and *Ernst*, by means of especial staining methods with *Löffler's* methylene-blue, hæmatoxylin, and *Platner's* nuclear black, have demonstrated the presence of *granules within different forms of bacteria*, which according to their behavior probably stand in some relation to the processes of division and spore-formation. *Ernst* designated the appearances seen by him as *sporogenous granules*, since he was able in certain bacteria to demonstrate their transition into spores; he is inclined to regard them as of the nature of cell-nuclei, a view which *Bütschli* also favors. *Bunge* regards the granules described by *Ernst* as cell-granules which have nothing to do with spore-formation, and describes other granules, which stain with *Löffler's* methylene-blue, as the forerunners of spores. *Marx* and *Woithe* regard the *Babes-Ernst* granules as not being nuclei in the ordinary sense of the word, but as representing products of the maximal condensation of the euchromatic substance of the cells, which are a sign of the highest intensity of vitality on the part of the cell. *Wagner*, on the contrary, holds that certain bodies, which he has observed in typhoid- and colon-bacilli, are nuclei.

According to *Nakanishi*, the spores form (in anthrax- and hay-bacilli) by a concentration of the chromophile substance about the nucleus, while the remaining portion of the protoplasm becomes clear; a membrane is then formed about the chromatin body, it takes on a fat-like shine, and loses its power to take stains (methylene-blue BB).

The bacteria are able to take the **carbon** necessary for their growth from most of the carbon compounds which are soluble in water. They can also derive their carbon from dilute solutions of substances which in greater concentration are injurious to them —as, for example, from benzoic acid, alcohol, salicylic acid, phenol, etc.

Their **nitrogen** is derived from *albuminous matter;* further, from those compounds designated as *amins* (methyl-, ethyl-, propylamin), *amido-acids* (asparagin, leucin) and *amides* (oxamide, urea), as well as from the *ammonia-salts* and in part also from *nitrates*. The albuminates, previous to their assimilation, are changed into peptone by means of a ferment given off from the bacteria. Free nitrogen cannot be assimilated as such. Nitrogenous and non-nitrogenous compounds are not only assimilable as such, but also in combination. The fission-fungi are able to take nitrogen from ammonia and nitric acid only in the presence of organic carbon compounds.

Sulphur, according to *Nägeli*, is essential to the schizomycetes, and they take it from sulphates, sulphites, and hyposulphites. The other *mineral substances* mentioned above are derived from various salts. If in the case of an abundance of nutrient

material there is too little water present, all further growth ceases; yet many of the fission-fungi are able to dispense with water temporarily. Spores suffer little from drying.

Many bacteria are very sensitive to **acids**, so that even a slight degree of acidity hinders their growth (for example, anthrax bacilli and the Fränkel-Weichselbaum pneumococcus). Others are able to grow with a moderate amount of acid in the nutrient fluid. As a general rule they are especially sensitive to mineral acids, but the presence of a large amount of citric, butyric, acetic and lactic acids hinders also their multiplication. In this connection belongs the fact that the products of decomposition caused by the fermentative action of the fungi are at a certain degree of concentration harmful to the development of the fungus, and finally stop its growth entirely. Thus, for example, in butyric-acid and lactic-acid fermentation the amount of butyric or lactic acid gradually formed finally checks the multiplication of the fungus. A similar result occurs in the bacterial putrefaction of albumin, since the products of the same, such as phenol, indol, skatol, phenylacetic acid, phenylproprionic acid, etc., hinder the further development of the bacteria. To alkalies the fission-fungi are less sensitive, and many can bear a rather high degree of alkalinity in the nutrient fluid, but there also exist forms which do not thrive in alkaline fluids (acetic-acid fungus).

According to the investigations of *Pfeffer* and *Ali-Cohen*, many motile bacteria show **chemotactic properties**—that is, they are attracted or repelled by certain chemical substances dissolved in water. Bacteria swimming about in fluids collect, therefore, at places where there are chemical substances which attract; for example, typhoid-bacilli and cholera-spirilla are attracted by potato-juice (*Ali-Cohen*). Potassium salts, peptone, and dextrin likewise attract, but the individual forms of bacteria behave very differently toward these substances (*Pfeffer*). Free acids, alkalies, and alcohol have a repelling action.

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§ 149. **The growth and multiplication of the fission-fungi give rise always to chemical transformations of the nutrient material,** which are brought about in part through the influence of *ferments produced by the bacteria,* and in part directly through the *metabolic processes occurring within the cells themselves.*

Among the **ferments** or **enzymes** are to be mentioned first the *proteolytic* or *albumin-dissolving enzymes* (*bacteriotrypsins*) which bring about a solution of the albuminous bodies and cause the disintegration of the peptone-molecule. Further, bacteria give rise to *diastatic ferments* which convert starch into sugar, also to *inverting ferments* which transform cane-sugar (disaccharid) into grape-sugar (monosaccharid).

The **chemical results of bacterial metabolism,** which are brought about by the vital activities of the fission-fungi aided by the enzymes

produced by them, consist in the first place of a decomposition of complex organic compounds. By many authors all these processes are designated as **fermentations,** while others (Lehmann) speak of fermentation only when a fission-fungus breaks down a given food-material with especial ease, thereby giving rise to one or more especial products in marked quantity, in association with or in place of its other metabolic products. Other authors still narrow the term fermentation to the decomposition of carbohydrates.

In the **decompositions caused by the fission-fungi very different products** are formed, which vary according to the composition of the nutrient material and the character of the fission-fungus. For the production of fermentation a proper fermentable material is necessary. Many fungi are able to cause fermentation in the presence as well as in the absence of oxygen, while to some of them a lack of oxygen is necessary.

Among the **products of bacteria** of especial importance to the physician are those which **have a poisonous action and cause tissue-changes,** to which belong particularly those substances which are described as *ptomaïns*, *toxins*, and *endotoxins*.

The **ptomaïns** are basic, crystallizable, nitrogenous products of the bacterial decomposition of albumin; they are also known as *putrefactive alkaloids* or *cadaveric alkaloids.* They show in part *poisonous properties.* The best known are sepsin, putrescin (dimethylethylendiamin), cadaverin (pentamethylendiamin), collidin (pyridine derivative), peptotoxin, neuridin, neurin, cholin, gadinin, and substances resembling muscarin.

The **true toxins** are specific bacterial poisons produced by pathogenic bacteria and are secreted by the latter, giving rise to the severe symptoms produced in diphtheria, tetanus, and sausage poisoning. The **endotoxins** are substances clinging to the bacterial cells that also have a poisonous action. In the bacterial cell there occur also the **bacterial proteins** which give rise to local tissue-necrosis and inflammation. The significance of these substances in the infectious diseases has already been mentioned in § 11.

Among other **decompositions produced by bacteria** the following are worthy of note: the formation of lactic acid, formic acid, acetic acid, propionic acid, butyric acid, often also the formation of alcohol and carbonic acid from sugar; the formation of acids (acetic, butyric, propionic, valerianic, succinic, formic, and carbonic) from alcohol and organic acids; the formation of indol, skatol, phenol, cresol, pyrocatechin, hydrochinon, hydroparacumaric acid, and paroxyphenylacetic acid (*von Nencki*, *Salkowski*, *Brieger*), and finally hydrogen sulphide, ammonia, carbonic acid, and water from albumin; the formation of ammonium carbonate from urea; the transformation of nitrous and nitric acids into free nitrogen; the reduction of nitrates to nitrites and to ammonia, etc. Finally, there are also bacteria living in the soil—the nitro-bacteria—which are able to form nitrous and nitric acids from ammonia (*Winogradsky*).

Along with the nitrification of nitrogen there occurs simultaneously a decomposition of earthy alkali carbonates, as shown by the fact that the nitrobacteria are able in the presence of organic carbon compounds to derive *from the carbonates the carbon necessary to the building-up of the cells.* There takes place, therefore, through the vital activity of these organisms, a synthesis of organic material out of inorganic substances.

Under the influence of the fission-fungi there are formed *bitter, sharp, nauseating substances* (bitter milk). Further, bacteria occasionally produce *pigments* of a red, yellow, green, blue, or violet color. For example, *Bacillus prodigiosus* produces a blood-red coating upon bread (bleeding bread); bandages and pus take on a bluish-green color as the result of the presence of the *Bacillus pyocyaneus.* In many cultures there is also formed a fluorescent coloring-matter.

The *phosphorescence* not infrequently seen upon decomposing sea-fish depends also upon bacterial products of decomposition, as has been shown by *Pflüger*, and appears when there is an active multiplication of the bacteria.

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See also § 11.

2. General Considerations Concerning the Pathogenic Schizomycetes and Their Behavior in the Human Organism.

§ 150. As has already been explained in § 11, there are among the schizomycetes numerous species which are capable of causing disease-processes in the human organism, and are therefore called **pathogenic schizomycetes.** The first condition of such action is evidently that the bacteria concerned must possess properties enabling them to multiply in the tissues of the living human body. They must therefore find in the tissues the suitable nutrient material, and in the body-temperature the

warmth necessary to their growth. The tissues, moreover, must not contain substances which are a hindrance to their growth (cf. § 31).

If pathogenic fission-fungi succeed in growing in the tissues of the body, if **infection** takes place (cf. § 11), their action is in general characterized by the production, *at the point of multiplication*, of *tissue-degenerations, necrosis, inflammation*, and *new-growths of tissue*, while at the same time the *toxins* produced by them cause *manifestations of poisoning.*

In individual cases the pathological processes vary greatly, in that the distribution of the bacteria in the organism, and their local action, as well as the production of the poisons, differ greatly with the different forms of bacteria.

With many the *local action* upon the tissue is the most prominent characteristic, with others the *general intoxication.* Many bacteria *confine themselves to the region in which they have gained entrance; others advance uninterruptedly upon the surrounding tissues;* others still are carried by the blood and lymph streams and lead to the formation of *metastatic foci*, and, finally, others *increase within the blood.*

If a spread of the bacteria takes place through the blood, the bacteria *may pass from the mother to the fœtus* during pregnancy, since the placenta forms no certain filter against pathogenic bacteria. This has been demonstrated, for example, in the case of anthrax-bacilli, bacilli of symptomatic anthrax, glanders-bacilli, spirilla of relapsing fever, typhoid-bacilli, the pneumococcus, and the tubercle bacillus. According to observations of Malvoz, Birch-Hirschfeld, and Latis, changes in the placenta, such as hæmorrhages, loss of epithelium, and alterations of the vessel-walls, favor the passage of bacteria. Moreover, bacteria—as, for example, anthrax-bacilli—can grow through the tissue-spaces. In general the passage of bacteria from the mother to the fœtus presupposes that, after the entrance of these organisms into the circulating blood of the mother, the latter shall remain alive at least long enough to allow of the passage of the bacteria into the fœtus.

The bacteria which succeed in multiplying within the human organism *die out again in many cases within a short time;* and the disease produced by them may proceed to *recovery* (cf. § 31). Nevertheless, it not infrequently happens that *they are preserved for a long time within the body*, and either *excite a continuous disease process*, or at times remain in a condition of inactivity, so that no pathological processes are recognizable until *after a longer or shorter period of latency, an active reproduction again takes place and manifestations of disease show themselves anew.*

Not infrequently a **secondary infection** associates itself with an infection already existing. The relation between the two infections is either that the second infection follows the first accidentally, or that through the first infection the soil is prepared for the second (cf. § 11).

Finally, there not infrequently occur **double infections**, in that two or more forms of bacteria develop coincidently in the tissues, and produce their characteristic injurious influence upon the latter.

Each pathogenic fission-fungus has a **specific action** upon the tissues of the human organism; but, nevertheless, *different species may exert a similar action.* For example, there are various bacteria capable of producing suppuration. Only in a certain proportion of cases do the pathological tissue-changes show such specific characteristics that from these the species of the pathogenic fission-fungus can be recognized with certainty.

Further, it has been demonstrated that **pathogenic properties of bacteria are by no means constant**; that, on the contrary, their viru-

lence varies, so that bacteria, which cause severe—that is, fatal—infections may become changed (weakened) through external influences, so that they either wholly lose their power of causing disease-processes in the organism, or at least cause only mild forms of disease. This peculiarity is not alone of theoretical interest, but is also of great practical importance. It explains to a certain extent, on the one hand, why a certain infection does not always run the same course, and, moreover, why along with severe attacks light ones also occur. On the other hand, it affords us the possibility of obtaining *material for inoculation* from attenuated cultures of bacteria, by means of which mild grades of infection or intoxication can be produced, which are able to protect the organism from severe infections or to bring about the cure of an infection already acquired (cf. § 32).

Weakening of the pathogenic properties of a fission-fungus can be brought about through the suitable action upon cultures of the same, by high temperatures, oxygen, light, or chemical antiseptic substances, as well as by the cultivation of the fungus in the body of a less susceptible animal. In some forms it is only necessary to cultivate the bacteria in question for some time upon artificial media (diplococcus of pneumonia), or to expose the culture to the air for some time (bacillus of chicken-cholera), in order to bring about an attenuation. If it is desired to preserve the virulence of the pneumococcus for some time, it is necessary, from time to time, to pass the bacteria cultivated upon artificial media through rabbits, which are very susceptible. The glanders-bacilli, tubercle-bacilli, and the cholera-spirilla lose virulence when cultivated uninterruptedly upon artificial media for some time. The streptococcus of erysipelas (Emmerich) becomes so attenuated through continued cultivation in bouillon or nutrient jelly that it is no longer capable of killing even mice.

As to the nature of the attenuation of virulence of bacteria by the methods mentioned above, it is possible to give only hypotheses. If the bacteria cultivated for a long time upon artificial media change in virulence, this may perhaps be explained in part by assuming that in a series of generations the less virulent varieties, which surely often arise, gradually gain the upper hand. For the attenuation of virulence by heat, chemical agents, etc., such an explanation is not adequate. In this case there is very probably a general weakening or degeneration of the protoplasm, and in harmony with this theory is the fact that such bacteria show a diminution in energy of growth.

If the presence of bacteria be suspected in any tissue-fluid or in the tissue-parenchyma, their demonstration may first be attempted by means of a **microscopical investigation.** Occasionally this is successful by the mere examination of a drop of the suspected fluid or of a smear preparation of the tissue-juice diluted with salt-solution or distilled water. In other cases it is necessary to employ staining methods, in which case cover-glass smears of the fluid are made and allowed to dry. The smeared cover-glass is then fixed by passing through the flame, and after cooling is stained. For this purpose methyl-blue is preferably employed, in a preparation of a concentrated methyl-blue solution in a [illegible] solution of caustic potash. Water solutions of fuchsin and methyl-violet are also frequently used. For many bacteria there are employed special staining methods, in which ordinarily the preparations are first overstained with a solution of gentian-violet or fuchsin in aniline water, or with a watery solution of methyl-violet, the excess of color then being removed by means of weak acids or by iodine and alcohol (Gram's method). In this way it is often brought about that the bacteria alone remain stained, often certain forms of bacteria only.

When it is desired to demonstrate the presence of bacteria in tissues, small portions of the tissue are hardened in formalin or in absolute alcohol, and are then cut into thin sections, which are stained by appropriate methods. Here again the

ethods most frequently employed are those mentioned above: gentian-violet, methyl-olet, and fuchsin. Good objectives are necessary for the microscopic examination; if ossible, oil-immersion lenses and illumination with substage condenser should be nployed.

If through any method the presence of **bacteria** in the tissue has been demon-rated, the attempt is next made to **cultivate** them. For this purpose the methods eveloped by *Koch* are usually employed. These, in principle, consist in obtaining st a fluid containing the bacteria, by means of scraping the tissue or by rubbing up eces of tissue in sterilized salt-solution. This fluid is then evenly distributed in a lution of gelatin or agar which has been liquefied by warming, and the mixture is ien poured upon horizontal glass plates, solidifying as it cools. The individual bac-ria, or spores, thus separated from each other develop in the firm nutrient medium.

By a proper application of this method there are obtained in the layer of gelatin arious colonies (Fig. 425), which differ in appearance so that they may often be differ-ntiated from each other by the naked eye alone. When sufficiently separated from ne another, the individual colonies may be taken up by means of a fine platinum eedle, and transferred either to a boiled potato, or to a sterile gelatin plate, or streaked pon the surface of the solidified nutrient fluid in a test-tube. Very often the infected eedle is stuck into the solidified transparent medium contained in a test-tube.

If the culture on the gelatin plate is pure, and if the entire procedure is carried out ith the necessary care and the avoidance of contamination, pure cultures may be ob-ained by this method. In stab-cultures, as well as in smear-cultures on potatoes or any ther nutrient medium, special peculiarities often show themselves which make it pos-

IG. 425.—Gelatin plate containing pellicle-like, sinuate colonies of small bacilli, and small, spherical, white colonies of cocci. Culture made from the exudate of a purulent peritonitis. Reduced one-third.

ible for the experienced observer to recognize the form of bacteria. At times, how-ver, it is necessary to make a thorough microscopic examination of the colonies.

It is evident that all the above manipulations must be carried out with care, and hat absolute cleanliness of the instruments used—glass-plates and test-tubes—as well s perfect sterilization of the nutrient medium are necessary. The proper methods of terilization in which a long-continued heating or an exposure to high temperatures lays an important rôle, are best learned in properly equipped laboratories. The neces-ary guidance is furnished in the various books on bacteriological methods of examina-ion, which have recently appeared.

An infusion of meat containing peptone and gelatin is commonly employed for naking plates. It consists of a watery infusion of chopped meat, to which a definite mount of peptone and salt is added. This is further neutralized with carbonate of oda, and enough gelatin is added to give a solid consistence at ordinary temperatures. 'or streak and stab-cultures this same gelatin is sometimes used; at other times a elly made of a mixture of a watery extract of meat, peptone, and agar-agar; or again lood serum which has been coagulated by warming.

For stab-cultures the jelly is allowed to solidify within the test-tube in a perpen-icular position; for streak-cultures the test-tube is kept in an oblique position until he jelly is set.

Sterilized bouillon is often used for cultures. The inoculated nutrient media are ept either at room-temperature or at higher temperatures in an incubating oven

(30°–40° C.). The proper nutrient medium to be used in individual cases must be determined by experiment. Experience has shown that the individual bacteria behave very differently in this respect, some growing best upon one, others upon another medium. To the nutrient medium there are often added with advantage such substances as sugar, glycerin, urine, brain-substance, etc.

It is self-evident that the processes briefly described above may be modified according to the necessities of the case. For example, in those cases in which it is necessary to grow the bacteria at high temperatures, the use of gelatin should be avoided and agar-agar plates should be made instead. Occasionally membranes or exudates from mucous surfaces (diphtheria) or small bits of excised tissue are placed directly into the culture-medium. When it is desired to examine the cultures directly under the microscope, cultures may be made upon glass-slides. In the case of many bacteria, as cholera-spirilla, the use of hanging-drop cultures is advised. In this method a drop of sterilized bouillon hangs down from the under surface of a cover-glass, and is inoculated from a previously cultivated pure culture of the fungus. The cover-glass is then placed over the excavation in a hollow ground-glass slide. Evaporation is prevented by the exclusion of the outer air from the cavity in the slide, by a rim of oil or vaseline placed beneath the edge of the cover-glass. By this method the multiplication of bacteria can be observed for a long time.

When *bacteria are sought in water*, a definite amount of the suspected water is distributed in gelatin, and plate-cultures are made. *Earth* is rubbed up with sterilized salt-solution; *air* is made to pass in definite amount through a sterilized salt-solution; and the salt-solutions thus infected are then mixed with gelatin, and from this gelatin plates are made.

The *culture of bacteria* on and in different media, accompanied by the microscopic examination of the different stages of development, *serves for a more exact characterization, and thereby for the differentiation of the species of the bacteria in question.* After its properties have been thoroughly studied in this way, the **influence of the bacterium upon the animal organism** is tested. As experimental animals, rabbits, dogs, guinea-pigs, rats, mice, and small birds are most frequently employed. The bacteria to be tested are introduced, sometimes under the skin, sometimes directly into the blood-current, sometimes by inoculation into the internal organs, sometimes by inhalation into the lungs, or sometimes by administration with the food into the intestinal canal. Bacteria can be regarded as pathogenic for a given animal when they multiply within the tissues and excite disease processes. If relatively large amounts are inoculated, the animal experimented upon may die under certain conditions, even if the bacteria do not increase at all in its body, since the poisonous substances formed in the culture and introduced by inoculation often suffice to kill the animal.

Experience has taught that only some of the bacterial infections which occur in man, when inoculated into animals, run the same course as in man, and, indeed, only those which also occur otherwise in animals. In other cases the pathogenic fission-fungi occurring in man or in certain animals are, it is true, pathogenic for the experimental animal, but the pathological process shows another localization and another course. In a third case the experimental animals are in part or wholly immune.

Inversely, fission-fungi that are often extremely pathogenic for the experimental animals are harmless for other animals or for man.

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II. The Different Forms of Bacteria and the Infectious Diseases Caused by Them.

I. The Cocci, or Sphærobacteria, and the Morbid Processes Caused by Them.

(a) *General Considerations Regarding the Cocci.*

§ 151. The **cocci** or **coccaceæ** (Zopf) are bacteria that occur exclusively in the form of round or oval or lanceolate cells. In their multiplication by division they often form peculiar aggregations of cells, which are commonly designated by special names according to the character of the different forms appearing. Since certain forms of cocci are especially likely to develop in definitely shaped aggregations, advantage has been taken of this fact, to classify them in different **species.** It should be noted, however, that a given species does not always appear in the same form, but may vary according to the nutrient conditions.

Many of the cocci multiply by division in one plane only—at right angles to the length of the elongated spherical cell. If the spheres resulting from division remain together for some time in the form of double spheres, and if this form appears with especial frequency in the case of any one species, it is designated as a **diplococcus**

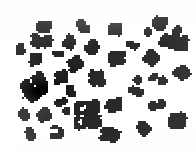

Fig. 428.

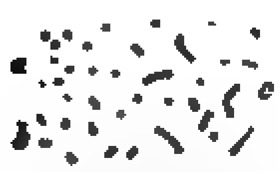

Fig. 426.

Fig. 427.

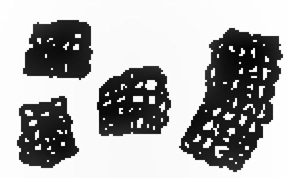

Fig. 429.

Fig. 426.—Streptococcus from a purulent peritoneal exudate of a case of puerperal peritonitis. *a*, Single cocci; *b*, diplococci; *c*, streptococci or torula-chains. × 500.

Fig. 427.—Colonies of micrococci in blood-capillaries of the liver, causing metastatic abscess-formation. From a case of pyæmia. Necrosis of liver-cells. × 400.

Fig. 428.—Cocci grouped in tetrads (merismopedia), from a softening infarct of the lung. × 500.

Fig. 429.—Sarcina ventriculi. × 400.

(Fig. 426, *b*). If, from a further continued division of the cells in one plane, rows of cocci (*torula chains*) result, these are known as **streptococci** (Fig. 426, *c*), and this term is used also as the name for a group. If the division of the cells takes place irregularly, and the cells remain together in small collections or heaps, the bacteria are usually designated as **micrococci** (Zopf) (Fig. 427). By Ogston and Rosenbach the name **staphylococcus** or *grape-coccus* has been used to indicate some of these forms. Larger collections of cells, which are held together by a gelatinous substance derived from the cell-membranes, have been designated as *zoöglœa* masses. If the masses of cocci are united into larger collections by means of a gelatinous envelope, they are spoken of as *ascococci* or *tube-cocci.*

To those cocci which remain united for a long time in a four-celled tablet (Fig. 428), the name of **merismopedia, tetracoccus** or **tablet-coccus**

was applied by Zopf. Others class such bacteria with the micrococci. The cocci that go by the name **sarcinæ** are characterized by division in three directions of space, so that compound cubical packets of spherical cells are formed from tetrads (Fig. 429).

The cocci not infrequently show a tremulous molecular motion in fluids; swarming movements have not been observed with certainty. Spore-formation has not been demonstrated in the majority of forms. According to Cienkowski, Van Tieghem, and Zopf, the *Coccus (leuconostoc) mesenterioides*, that produces a frog-spawn-like culture on sugar or parsnips, forms arthrogenic spores, in that some particular cell in a torula chain becomes larger and glistening. According to Prazmowsky the *Micrococcus ureæ* also forms spores.

The **saprophytic cocci** grow upon very different nutrient substrata and cause by their growth in suitable media various processes of decomposition. Many also form pigments. *Micrococcus ureæ* causes a fermentation in urine by means of which ammonium carbonate is formed from the urea. *Micrococcus viscosus* is the cause of the slimy fermentation of wine. The cause of the *phosphorescence of decomposing meat* was found by Pflüger to be a micrococcus that forms slimy coatings on the surface of the meat.

Of the pigment-producers the best known are *Micrococcus luteus, Micrococcus aurantiacus, Sarcina lutea, Micrococcus cyaneus* and *Micrococcus violaceus*, which, when grown upon boiled eggs or potatoes, produce yellow, blue, and violet pigment respectively.

Saprophytic cocci are found in the mouth cavity and intestine, as well as on the surface of the skin, and occasionally also in the lungs. *Micrococcus hæmatodes* (Babes) is said to be the cause of red sweat, and forms red zoöglœa masses.

Sarcina ventriculi (Fig. 429) occurs not infrequently in the stomach of man and animals, especially when abnormal fermentations are going on. According to Falkenheim the stomach sarcines can be cultivated upon gelatin, and form in this medium round, yellow colonies, which contain colorless monococci, diplococci, and tetrads, but never cubical packets. They form these, however, in neutralized hay-infusion, and their growth causes a souring of the infusion. The membrane of the sarcinæ is said to consist of cellulose.

Microcococcus tetragenus (*merismopedia*) is not infrequently found in human sputum, and in the mouth and throat; it may be present further in the wall of tuberculous cavities, or in hæmorrhagic or gangrenous foci of the lungs. It forms tetrads (Fig. 428) whose cells are held together by a gelatinous membrane. On gelatin-plates it forms round or oval, lemon-yellow colonies. It is pathogenic for white mice and guinea-pigs, to a less extent for rabbits, and, when injected subcutaneously, excites purulent inflammations, in the mouse often also a septicæmia. Intratracheal injections may give rise to inflammations of the respiratory passages and the lungs.

The **pathogenic cocci** cause acute inflammations which usually heal after the death of the bacteria; but it not infrequently happens that cocci may remain in the body for a long time and give rise to chronic processes.

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See also § 148.

(*b*) *The Pathogenic Cocci.*

§ 152. The **Streptococcus pyogenes** (Rosenbach) is a coccus which, in multiplying, forms *double spheres* and *chains of spheres* (Fig. 426) of different lengths, containing from four to twelve or more cells. This chain-formation comes to an especially full development when the streptococcus is growing in fluids—in nutrient bouillon or fluid exudates—but is also usually seen when it is growing within the tissues.

The cocci stain well by Gram's method, are facultative anaërobes, grow best at 37° C., and form small whitish colonies on gelatin and agar.

Streptococcus pyogenes causes in man **inflammations,** *which usually, though not always,* assume a **purulent character.** Occasionally it is found also upon normal mucous membranes, for example, in the upper air-passages, or in the vagina and cervix uteri; it may therefore be assumed in such cases that its virulence is very slight, or that the mucous membranes offer a successful resistance to its entrance into their tissues.

An infection with streptococci may occur either in healthy individuals, or in those who have received some injury, or finally as an accompaniment and sequela of other infections, particularly of scarlet fever, smallpox, diphtheria, and pulmonary tuberculosis.

If the streptococcus multiplies upon the *surface of mucous membranes*—for example, of the respiratory tract (Fig. 430)—it excites an *inflammation,* which may bear the character of a *desquamative* or *purulent catarrh* (*c*), or of a *croupous exudation* (*d*). If it penetrates into the connective tissues of the submucosa, it causes most frequently inflammations which are *phlegmonous* in character—i.e., a more or less quickly spreading, seropurulent, or purulent, or fibrinopurulent, or serofibrinous inflammation, which may at certain points lead to suppuration and abscess-for-

mation. In the exudate the cocci may be found in part free (Fig. 431, *c*), or in part inclosed within cells (*b*).

FIG. 430.—Streptococcus tracheitis in scarlet fever (alcohol, carmine, methyl-violet, iodine). *a*, Connective tissue; *b*, desquamated epithelium; *c*, membrane composed of cells and streptococci; *d*, fibrin-threads. × 300.

The multiplication of streptococci in the stratum germinativum of the skin leads to the necrosis of epithelium and the formation of *purulent vesicles* or *blebs*.

If the streptococcus spreads in the *corium*, into which it penetrates especially in the case of small wounds of the skin, it utilizes the lymph-spaces and lymph-vessels (Figs. 432, *a*; 433, *h*, *i*; 434, *c*) as pathways and as places for the development of colonies, causing a more or less severe inflammation, which is characterized macroscopically by an advancing redness and swelling of the skin known as *erysipelas*. To the external appearances there corresponds a more or less severe serous and cellular infiltration (Figs. 432, *d*, *e*, *f*; 433, *m*; 436, *c*), and often also a fibrino-cellular exudation (Fig. 433, m_1). The infection of the lymph-vessels in erysipelas involves at times chiefly the superficial layers of the cutis (Fig. 433), at other times the deeper layers (Fig. 434, *c*). In the latter case the erysipelatous process becomes phlegmonous in character, so that between the two processes a sharp border-line cannot be drawn. At the same time with the infection of the

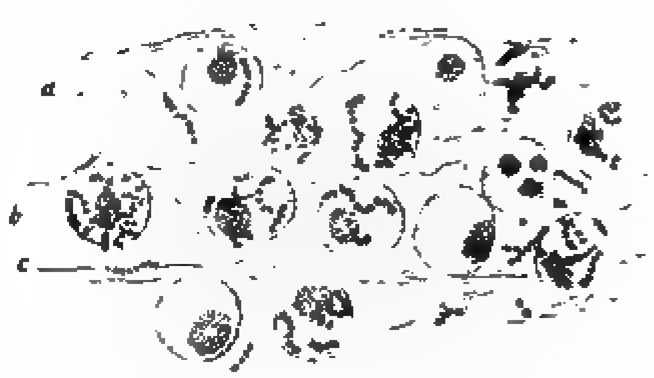

FIG. 431.—Streptococcus pyogenes from a phlegmonous focus of the stomach (alcohol, carmine, methyl-violet, iodine). *a*, Leucocytes; *b*, leucocytes containing streptococci; *c*, free streptococci. × 500.

FIG. 432.—*Streptococcus erysipelatis* (*a*) inside a lymph-vessel (*b*), in part composed of thickly crowded spheres, in part of torula-chains (alcohol, gentian-violet); *c*, neighborhood of the lymph-vessel, with pale, non-staining nuclei; *d*, vein; *e*, perivenous cellular infiltration of tissue; *f*, accumulation of cells in the lymph-vessel. Section of rabbit's ear two days after inoculation with erysipelas-cocci. × 225.

deeper layers streptococci may spread on the surface of the epithelium —that is, beneath the horny layer (Fig. 434, g), and cause a loosening of the epithelial cells and a desquamation of the horny layer (f).

FIG. 433.—Section of the skin in erysipelas bullosum (alcohol, alum-carmine). *a*, Epidermis; *b*, corium; *c*, vesicle; *d*, covering of vesicle; *e*, epithelial cells containing vacuoles; *f*, swollen cells with swollen nuclei; *g*, g_1, cavity caused by the liquefaction of epithelial cells, and containing fragments of epithelium and pus-corpuscles; *h*, lymph-vessel, partly filled with streptococci; *i*, lymph-vessel filled full of streptococci; *k*, colony of streptococci in the tissue; *l*, l_1, necrotic tissue; *m*, cellular, m_1, fibrinocellular infiltration; *n*, fibrinocellular exudate in the vesicle. × 60.

FIG. 434.—Erysipelas of the head in a child of one month of age (bacterial staining, carmine). *a*, Cutis with hair-follicles; *b*, subcutis; *c*, lymph-vessel with streptococci and inflamed surrounding area; *d*, rete Malpighii; *e*, *f*, horny layer; *g*, streptococci lying upon the rete Malpighii. × 45.

[illegible] streptococci the pro[illegible] [illegible] of the epithelium. Fig. 438, [illegible] [illegible] erysipelas bullosum, or to ne-

FIG. [illegible]—[illegible] of the [illegible] connective tissue; [illegible]

crosis and gangrene of the [illegible] erysipelas gangrenosum [illegible] [illegible] of the tissue.

In the [illegible] tissue the [illegible] and multiplication of the [illegible] Fig. [illegible] [illegible] to a progressive [illegible] and fibrinopurulent inflammation, often with [illegible] suppuration. Such forms of infection are known as [illegible].

In the [illegible] the streptococci increase and spread [illegible] in the connective tissue of the perimysium [illegible] into the sarcolemma-tubes [illegible] the [illegible] are more or less severe inflammations [illegible].

[illegible] [illegible] causes purulent or croupous [illegible] hæmorrhagic [illegible] alveoli.

Should [illegible] from the skin or from a mucous membrane—as [illegible] the [illegible]—they may increase [illegible] very large numbers in the marrow tissue [illegible], *a*, *b*, and here give rise [illegible] necrosis and also to a purulent inflammation [illegible] the neighbouring tissues.

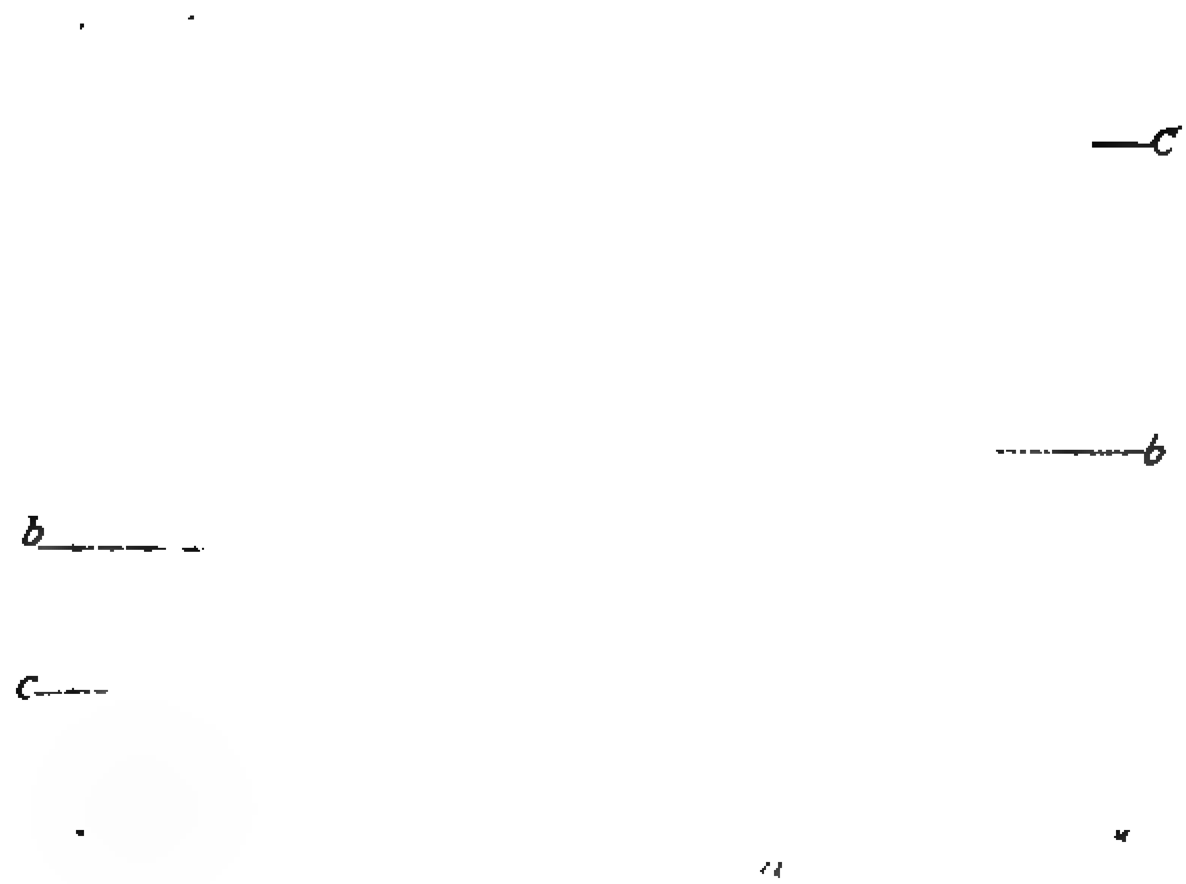

FIG. 436.—Streptococcus phlegmon in muscle. (Alcohol, Weigert's stain.) *a*, Masses of streptococci; *b*, leucocyte infiltration; *c*, transverse section of muscle-fibres. × 100.

FIG. 437.—Streptococcus infection of the petrous portion of the temporal bone, from a child of eight months of age (formalin, nitric-acid decalcification, carmine, methyl-violet). *a*, Medullary spaces completely filled with streptococci; *b*, beginning invasion by streptococci; *c*, bone marrow; *d*, trabeculæ of bone. × 300.

A streptococcus infection may terminate, either sooner or later, in that the opposing forces of the organism restrict the further spread of the bacteria, and destroy them. Not infrequently, however, the infection progresses up to the time of death.

If the streptococci break into the lymph- and blood-vessels, *metastases* are often formed, and distant organs are in this way involved. *Infection of the lungs* leads easily to infection of the *pleura*. Infection of the *female genital tract*, which easily takes place during delivery and the puerperium, leads very often to a spread of the infection to the *peritoneum* by means of the lymphatics. Infection of the *serous membranes* leads usually to a seropurulent, or fibrinopurulent exudation, the streptococci developing luxuriantly in the free exudate, and forming long chains. In infection of the blood, the streptococci do not increase in the circulating blood, but at the points where they come to rest; in the small capillaries of the lungs, heart, liver, kidneys, spleen, bone-marrow, joints, etc., or even on the valves of the heart. At the point of increase there is likewise produced an inflammation, which in general bears the same character as the primary inflammation, but is not infrequently less severe and more circumscribed.

Hæmatogenous streptococcus-infection of the lung leads to the formation of inflammatory foci (Fig. 438, *a*), which for the greater part show a

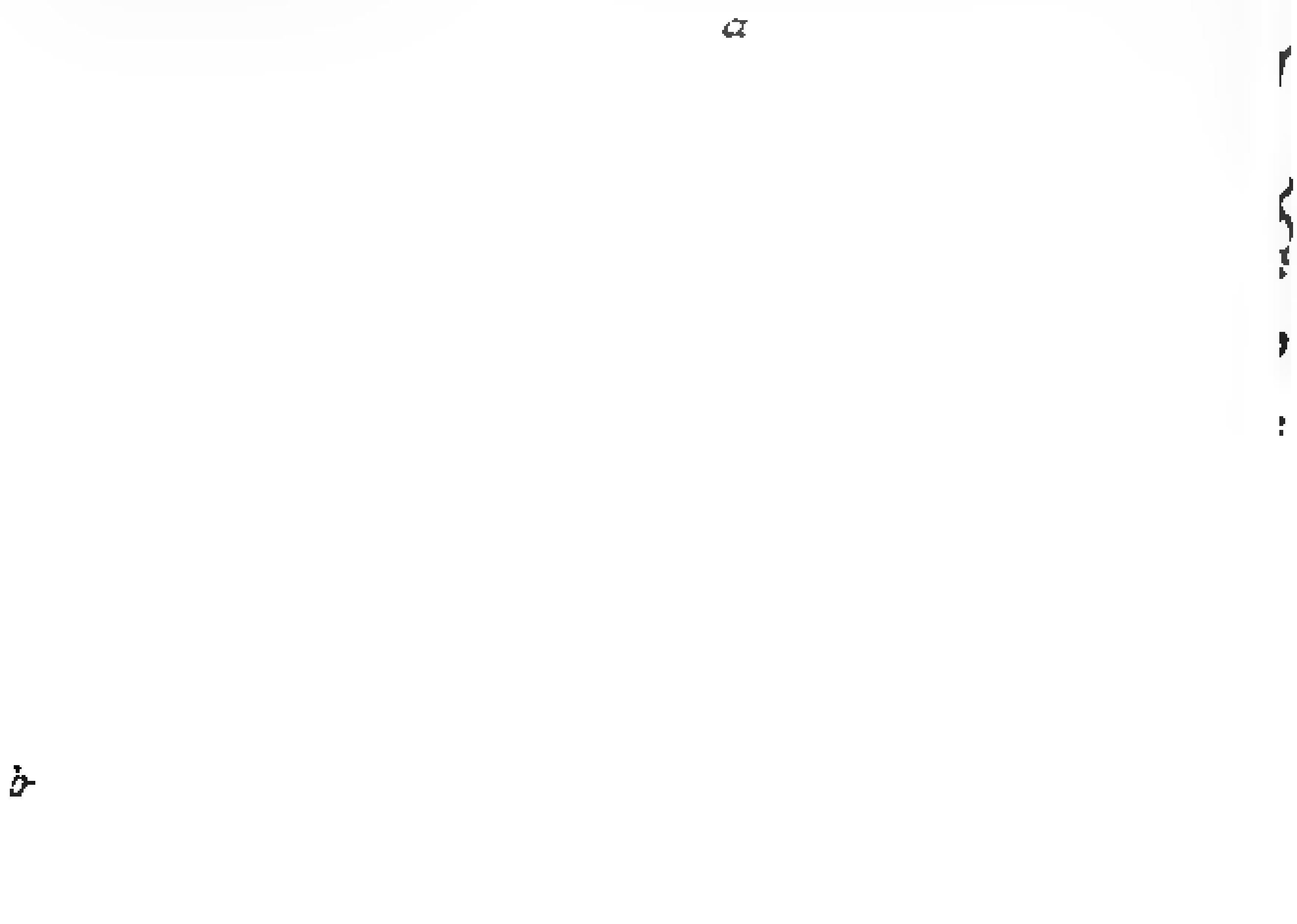

FIG. 438.—Metastatic hæmatogenous streptococcus pneumonia, after angina (alcohol, alum-carmine, methyl-violet, iodine). *a*, Pneumonic focus with (blue) streptococci; *b*, slightly inflamed lung tissue about the focus. × 50.

central suppuration. Collections of streptococci on the *surface of the endocardium* of the valves or of the heart wall (Fig. 439, *a*) lead to a superficial necrosis and further to the formation of coagula (*b*), collections of leucocytes (b_1) and proliferations of granulation tissue (*c*, *d*). A deeper infection with the streptococci causes an extensive necrosis of the tissue accompanied by an inflammation of the surrounding tissues.

streptococci are carried by the blood-stream into the coronary arteries, ere are produced in the heart-muscle inflammatory foci, which are ually purulent in character.

FIG. 439.—Endocarditis of the wall of the left auricle, due to streptococci (alcohol, methyl-violet, carne). a, Masses of cocci; b, b_1, leucocytes and coagula; c, area of proliferation; d, inflamed endodium. × 100.

FIG. 440.—Erythema multiforme, due to streptococcus infection, arising in the middle ear (Fig. 437), om a child eight months old. Section through a red spot in the skin of the back of the foot (alcohol, ethyl-violet, carmine). a, Corium; b, subcutaneous tissue; c, capillaries filled with streptococci. × 46.

If the cocci pass to a blood-vessel of the skin or subcutaneous tissue, they may increase in the same to such an extent that they form perfect casts of the capillaries (Fig. 440, *c*). As the result of the surrounding hyperæmia there are produced in the skin red spots and swellings, and eventually purulent foci. In the *kidneys*, in whose vessels there often occurs an extraordinary multiplication of streptococci (Fig. 441, *a*, *b*),

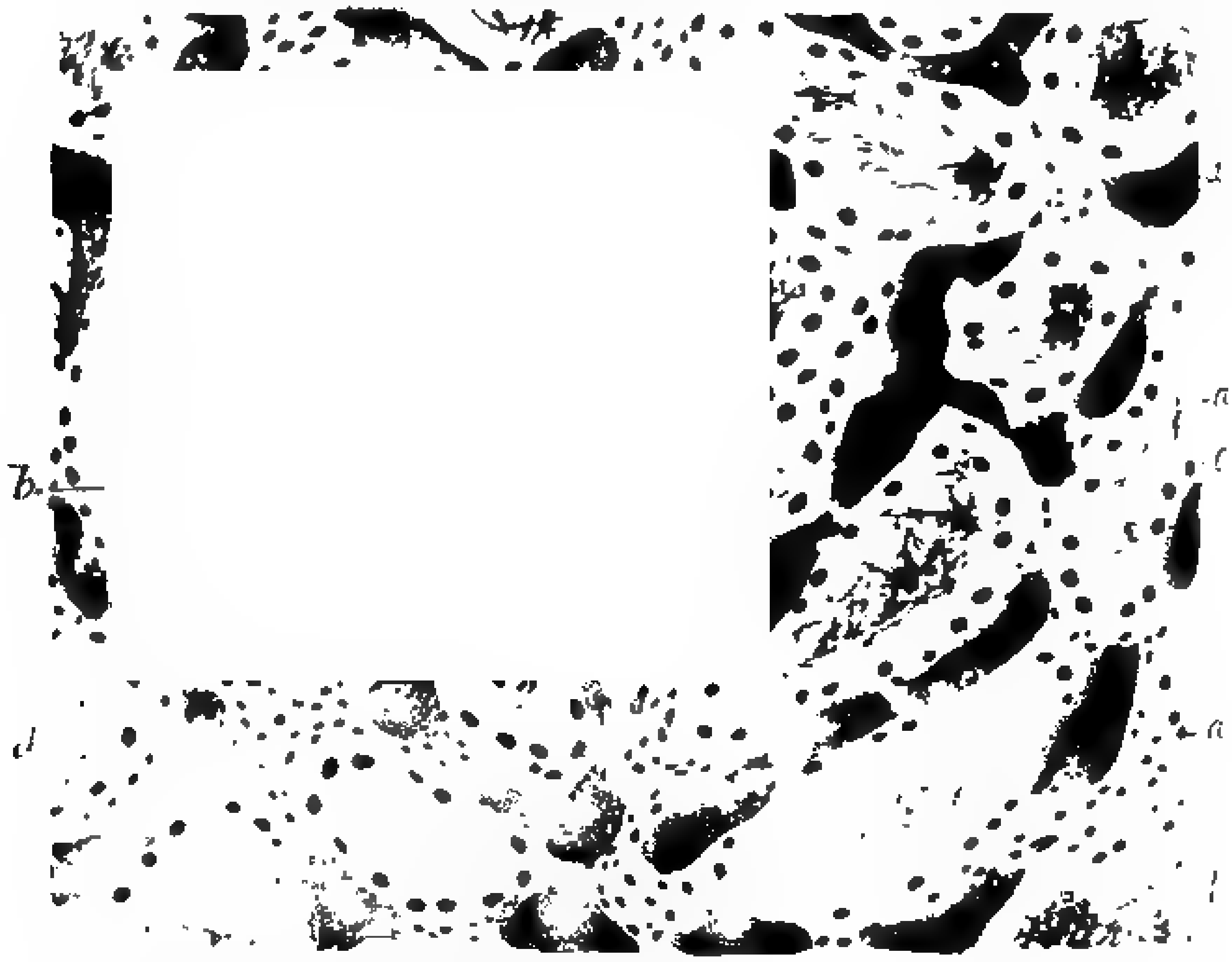

FIG. 441.—Extreme streptococcus infection of the kidney (grayish areas), arising after streptococcus angina (alcohol, Weigert's stain). *a*, Cocci in the intertubular, *b*, in the glomerular capillaries; *c*, urinary tubules; *d*, fibrin in the urinary tubules. × [illegible]

there arise in the first place grayish-yellow circumscribed areas of discoloration, which are dependent upon the collection of bacteria, the local anæmia, tissue-necrosis, and often a beginning serofibrinous exudation (*d*). Later, yellow discolorations and softening of tissue appear, corresponding to suppuration. Similar changes may be demonstrated also in other organs.

The *danger of a streptococcus infection* depends partly upon *the severe progressive local changes* and the *formation of metastases*, and partly upon the accompanying *intoxication*, which finds expression in the fever and the severe general symptoms. If the symptoms of intoxication are very prominent the condition is designated **septicæmia**. A predominance of metastatic suppuration leads to the form of disease designated as **pyæmia**. A combination of both conditions is known as **septicopyæmia** or **pyosepthæmia** (cf. § 11).

The course of a streptococcus infection, as well as the mode of entrance of the cocci into the body, can usually be recognized, since the infection ordinarily starts in the injured outer skin or from deeply pene-

trating wounds, from the mucosa of the upper digestive and respiratory tracts, or from the genital apparatus as the result of changes due to childbirth. **Cryptogenic infection** is, however, not rare; in such cases the first symptoms recognizable or at least noticed clinically are those dependent upon the disease of an internal organ, so that it appears as if the infection was primary in this organ.

The individual foci of disease in streptococcus infection may present very different degrees of severity of inflammation; and this is dependent partly upon the virulence of the bacteria, partly upon the individual differences of the infected persons, partly upon the seat of the infection, and partly upon the influence of preceding or accompanying pathological conditions. As regards this last factor it may be noted that many infectious diseases (diphtheria, scarlatina, smallpox, tuberculosis, typhoid fever, influenza) which lower the body resistance increase the predisposition to streptococcus infection. In the case of the growth of streptococci upon the surface of the endocardium, the inflammation often bears a very pronounced proliferative character (Fig. 439, *d*, *c*). In hæmatogenous streptococcus-dermatitis (Fig. 440) the process may cease with the formation of red spots. Phlegmons, which usually run a rapid course and lead in a short time to tissue-necrosis and suppuration, may also have a very chronic course, particularly in the neck, and are then characterized by a progressive swelling and induration of the affected area, so that the affection may be designated a "*wooden phlegmon*" (Reclus). Fever may be wholly absent. The process consists of a progressive proliferation of granulation tissue and a new-formation of connective tissue due to streptococci (or staphylococci), while suppuration is absent or confined to circumscribed areas.

The biological characteristics of the *Streptococcus pyogenes* are very variable, and this is well shown both in its behavior as a disease-producing agent and in the cultures of streptococci taken from different cases. Consequently an effort has been made to divide the streptococci into different species, and in particular has the streptococcus which causes erysipelas been regarded as a distinct form—the *Streptococcus erysipelatis*. Further, according to the place in which the streptococcus was found, it was formerly customary to speak of a *Streptococcus puerperalis* (*Arloing*), *Str. articulorum* (*Flügge*), *Str. scarlatinosus* (*Klein*); or, according to the manner of growth, of a *Str. longus* and *Str. brevis*, etc. (*von Lingelsheim*). These characteristics are, however, not sufficient to form a basis for the separation of the streptococci into different species; and it appears more correct, or at least more expedient, to consider all the chain-forming strepococci as one species, which appears in many varieties. According to *Howard* and *Perkins* (*Jour. of Med. Research*, 1901) there is a small group of pathogenic capsulated streptococci characterized by the viscidity of their growth and by the formation of gelatinous exudations in animals. For this group they propose the name of *Streptococcus mucosus*.

In diphtheria and scarlet fever, streptococcus infections of the throat and air-passages are extremely common, particularly in the case of the first-named, so that many authors (*Baumgarten*, *Dahmer*) are inclined to assign to the streptococcus a co-ordinate position with the diphtheria-bacillus in the causation of diphtheria—the diphtheria-bacilli predominating in the lighter forms of infection, the streptococci in the more severe. Pure streptococcus infections may present the same picture as that produced by the *Loeffler's* bacillus. If both forms of bacteria are present, their effects may be combined; perhaps also the presence of streptococci increases the virulence of the diphtheria-bacilli.

The *Streptococcus pyogenes* is especially pathogenic for mice and rabbits (much less so for dogs and rats); but its virulence varies greatly, and rapidly decreases in cultures grown on ordinary media. Its virulence is retained for a relatively long time (*Marmorek*) in cultures of the cocci in human- or in horse-serum (serum two parts, bouillon one part), or in a mixture of bouillon and ascitic fluid.

The **nature of the poisons produced by streptococci** is not known. It has been definitely determined that filtered cultures sterilized at 65–70° C. contain poisons;

but it is not yet known whether this poison, like the toxin of the diphtheria-bacillus, produces an antitoxin in the organism and therefore should be regarded as a true toxin.

According to *Simon* there can be distinguished an intracellular weakly virulent poison and a toxin excreted by the streptococcus. The latter, however, is produced only under certain conditions as, for example, under the influence of the bactericidal juices of the animal body. Under certain conditions the streptococcus can also produce hæmolysin.

Numerous investigators (*Neufeld, Rimpau, Tavel, Menzer, Aronson, Marmorek, Moser*, and others) have attempted to immunize animals against streptococci and to produce an antistreptococcus serum, and the sera thus obtained have been used in the treatment of streptococcus affections in man. At the present time it is not possible to judge as to the therapeutic value of these procedures. One serum obtained from immunized horses, according to the method of Dr. Aronson, is manufactured in the chemical works at Actien (C. Schering). According to *Neufeld* and *Rimpau*, the serum acts upon the bacteria, changing them so that they are taken up by the cells.

A number of writers regard a small micrococcus (*Diplococcus rheumaticus*) as the cause of rheumatic fever (see article by *Poynton*, Osler's "Modern Medicine," vol. ii.). *Cole* and others have shown that various streptococci produce experimental endocarditis and arthritis, and they, therefore, hold that there is no specific variety for this affection.

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§ 153. The **Diplococcus pneumoniæ** (Fränkel, Weichselbaum), or **Streptococcus lanceolatus** (Gamaleïa), or **Diplococcus lanceolatus** (Foà, Bordoni-Uffreduzzi), and also known as the *Pneumococcus*, is a pathogenic treptococcus of very frequent occurrence. It forms spherical, oval, and anceolate cocci (Fig. 442, *a*), which in the human body are usually surrounded by a transparent capsule, and are grouped together in pairs (*b*, *d*), or more rarely in chains of such pairs (*c*), or in large colonies (*d*).

The Diplococcus pneumoniæ stains well with fuchsin and with gentian violet, and by these stains the capsule may be demonstrated in smear-preparations. The cocci are also stained by Gram's method.

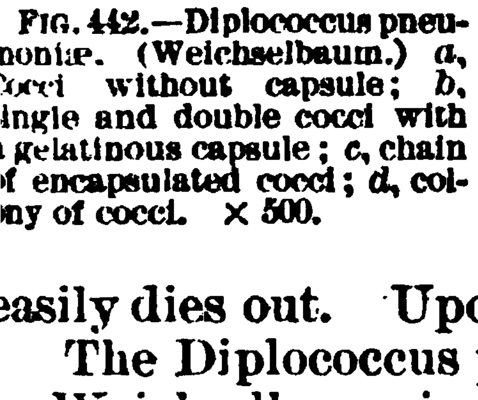
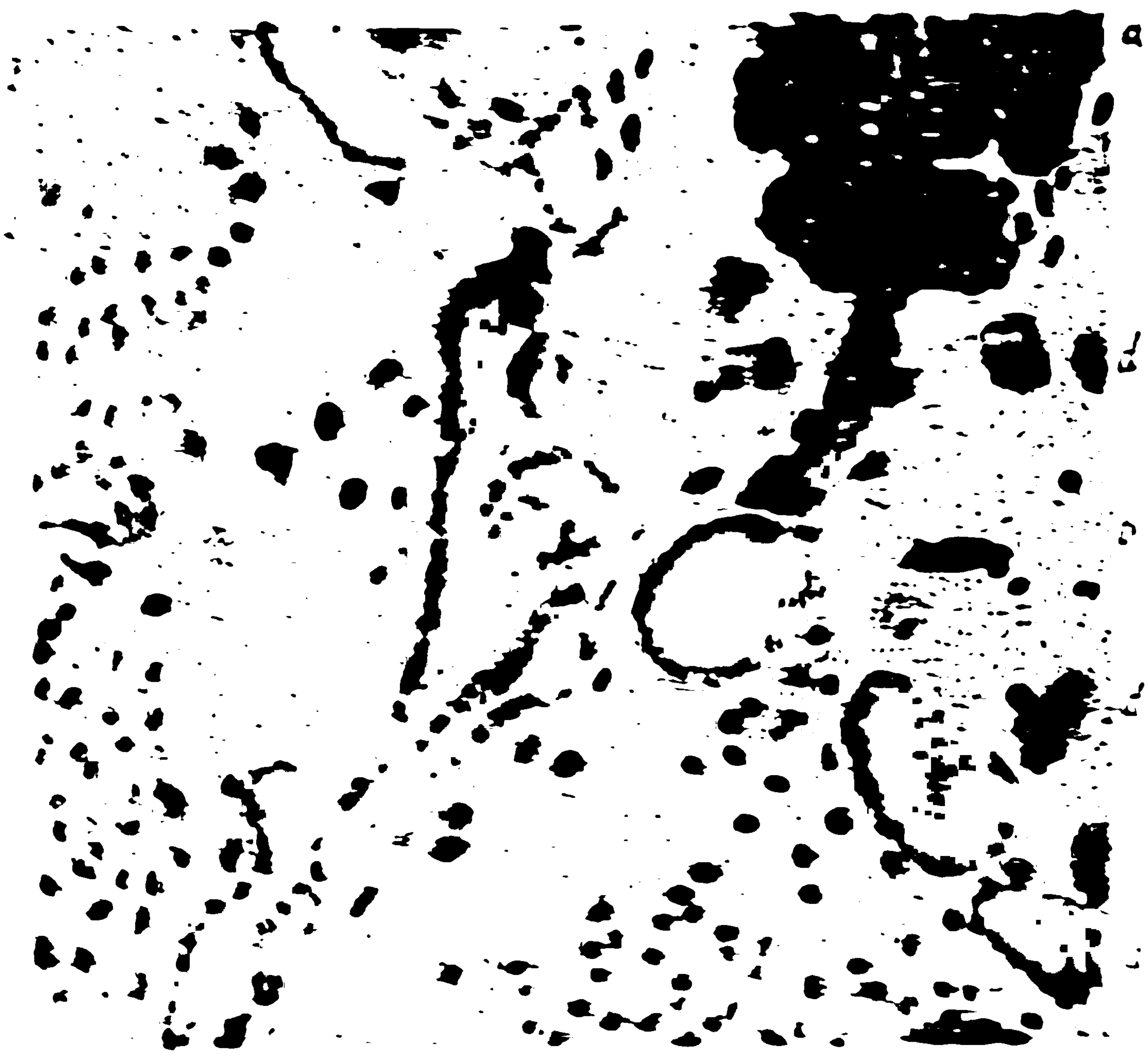


FIG. 442.—Diplococcus pneumoniæ. (Weichselbaum.) *a*, Cocci without capsule; *b*, single and double cocci with a gelatinous capsule; *c*, chain of encapsulated cocci; *d*, colony of cocci. × 500.

The cocci are facultative anaërobes. They will not grow upon gelatin at ordinary room-temperature, but do so upon slightly alkaline blood-serum-gelatin, upon agar and in bouillon, at a temperature above 22° C., and best at the temperature of the body. They form upon the surface of the medium a delicate, translucent, glistening culture, which suggests the dew-like deposit of moisture upon a cover-glass (Fränkel); and consists of diplococci and chain-cocci without capsules. The growth is, however, scanty; and easily dies out. Upon potatoes the cultures do not thrive.

The Diplococcus pneumoniæ is in a great number of cases (according to Weichselbaum in seventy-one per cent.) the cause of the affection of the lung known as *croupous pneumonia*, in which the lung is the seat of an acute inflammation which is ushered in by a congestive hyperæmia (Fig. 443, *a*). In the course of the disease the alveoli over large areas of the lung become filled with a coagulated exudate consisting of desquamated epithelium, leucocytes, red blood-cells, serous fluid and fibrin (Fig. 204). In the normal course of the disease the exudate becomes liquefied and absorbed. As has been shown by numerous observations, the Diplococcus pneumoniæ may also cause in the lungs other inflammatory processes bearing the character of a catarrhal or croupous bronchopneumonia. During the course of the disease the cocci are found especially in the inflamed areas, in the greatest numbers at the beginning of the inflammation; they lie in part free in the alveoli (*b*) and in part clinging to

cells (*d*). They are found also in parts of the lung bordering upon the inflamed area, in the pleura, and under certain conditions also in the pericardium, peritoneum, meninges, accessory nasal cavities, cellular tissue of the neck, in the mediastinum, submucosa of the soft palate and pharynx, in the conjunctiva, and the skin. In all these places they may give rise to inflammatory changes. At times they may be demonstrated in the juice of the spleen, and in the blood, and in pregnant women may pass into the fœtus (Viti). Under certain circumstances they may be widely distributed throughout the body, and may cause, in the meninges, pleura, pericardium, and peritoneum, fibrinous, serofibrinous, and at times seropurulent and fibrinopurulent inflammations, without giving rise to a pneumonia. Further, they may cause inflammation of



[illegible]

the conjunctiva, middle ear, endocardium, kidneys, joints, tubes, endometrium, [illegible], bone-marrow, and periosteum, and these inflammations may lead to suppuration. In many cases the mouth and nasopharynx appear to be the avenue of entrance—in these regions the cocci are not infrequently found, even in healthy individuals. Correspondingly, in [illegible] meningitis Weichselbaum [illegible] the ethmoid labyrinth often [illegible]. They are found in the exudates in all the [illegible]; and the gelatinous capsule may present a [illegible]

[illegible]

skin of the rabbit's ear (*Neufeld*) they also produce erysipelatous inflammations. Rabbits are especially susceptible, as they die with symptoms of septicæmia in from thirty-six to forty-eight hours after subcutaneous inoculation. The injection of pure cultures into the pleural cavity of rabbits gives rise to a pleuritis as well as a splenization of the lung, in which the parenchyma of the organ is filled with a hæmorrhagic serous exudate.

According to *A. Fränkel* the cocci very easily lose their virulence, particularly when cultivated upon milk; and if it is desired to retain their virulence they must, from time to time, be passed through susceptible animals. Cultivation of the cocci at 42° C. for one to two days destroys their virulence.

There still exist different views as to the rôle which the *Diplococcus pneumoniæ plays* in meningitis. According to the investigations of *Weichselbaum, Jaeger, Foà, Albrecht and Ghon, Councilman, Mallory and Wright*, and others, it may be regarded as definitely demonstrated that the *Diplococcus pneumoniæ can also cause meningitis*, and that there exists also a coccus, the **Diplococcus intracellularis meningitidis** (*Weichselbaum*), which is different from the pneumococcus and is to be regarded as the *cause of epidemic cerebrospinal meningitis.* According to *Jaeger*, this organism does not grow like the streptococci, but forms heaps like the staphylococci. *Albrecht, Ghon*, and *Weichselbaum* point out its great similarity to the gonococcus. They propose to call it in the future the **Micrococcus meningitidis cerebrospinalis.** It is found in the nasal secretions of cases of epidemic meningitis and also in that of individuals coming into contact with such cases. In the inflammatory cerebrospinal exudate it is found particularly in the polynuclear leucocytes. The essential pathological lesions are inflammatory changes in the membranes of the cord and brain, and in the tissue of the brain, cord, and nerves. *Flexner* and *Jobling* (*Jour. Amer. Med. Assoc.*, July, 1908) report most encouraging results in the treatment of epidemic meningitis with a serum prepared in the horse by inoculation of *Diplococcus intracellularis.*

Pneumotoxin is formed by the pneumococci most abundantly in the human and animal organism, but only sparsely in ordinary nutritive media (*Isaeff*). It is doubtful whether bactericidal antibodies or antitoxins arise during the course of the disease. It is therefore probable that the pneumotoxin does not belong to the true toxins. *Animals may be immunized* in various ways against pneumococci, and the serum of an immunized animal may be used also as a healing serum. The results of treatment in man are still doubtful. Difficulties arise through the fact that pneumonia can be caused also by various other bacteria (pneumo-bacilli, pus cocci, influenza-bacilli, etc.). (See *v. Marikovsky* and *Oppenheimer, l. c.*)

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FIG. 444.—Multiple abscesses of the skin, due to staphylococci (alcohol, carmine, Gram's method). Child of three weeks. *a*, Epithelium; *b*, corium; *c*, hair-follicle; *d*, *e*, purulent foci with cocci. × 40.

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§ 154. The **Staphylococcus pyogenes aureus** (Rosenbach) or **Micrococcus pyogenes** (Lehmann) consists of spherical cells occurring singly

r in pairs, and by their multiplication forming grape-like clusters and warms. The cocci are easily stained by various aniline dyes, and also y Gram's method. They are facultative anaërobes, but grow better hen supplied with oxygen.

The staphylococcus thrives on all culture-media, even at ordinary oom-temperatures, though better at 37° C. It forms white colonies, hich produce pigment in those parts exposed to the air and become range-yellow. The pigment-formation is most marked on agar and otatoes. Gelatin is slowly liquefied. In the presence of grape-sugar forms lactic acid, acetic acid, and valerianic acid. In bouillon-cultres there are produced poisons of very violent action. The Staphylococcus pyogenes is one of the most frequently occurring pathogenic bacria, and is, with the Streptococcus pyogenes, the most common cause of **uppuration.** Both forms of cocci are therefore designated **pus-cocci,** the narrower sense of the term. It is widely distributed throughout e external world, and has been demonstrated in milk, wash-water, and aste-water, as well as in the air of operating-rooms and sick-chambers.

b

c

G 445.—Miliary purulent nephritis, caused by staphylococci, primary focus in skin (furunculosis) (alcohol, methyl-violet, carmine). *a*, Normal kidney tissue; *b*, collections of cocci; *c*, purulent focus. × 40.

ncreasing in the tissues of the human body (Figs. 444–446) it causes *ssue-degenerations* and *tissue-necroses* followed by *inflammation* (Figs. 444, *e*; 445, *b*, *c*; 446, *c*, *d*), which is usually *purulent in character*, but not ifrequently is less severe—that is, it *does not lead to tissue-suppuration.*

The *suppurations* produced by staphylococci are usually *circumscribed* Figs. 444, 445), and show a less tendency to involve rapidly the surounding tissue than do the suppurations caused by streptococci. In the kin they give rise in particular to the forms of inflammation known as

acne, *eczema*, *furuncle*, and *cutaneous* and *subcutaneous abscesses*. In the osseous system they are the most frequent cause of the hæmatogenous purulent diseases of the bone marrow and periosteum known as *septic osteomyelitis* (Fig. 446) and *periostitis*. They not infrequently cause *purulent inflammations of the liver, lungs, pleura, peritoneum, brain, meninges, muscle, myocardium, spleen, kidneys, joints*, etc.; and are often the cause of severe, in part purulent, *inflammations of the endocardium*. Since the virulence of the staphylococci varies, they can also produce, in all the regions named, *lighter transitory inflammations* which heal with or without scar-formation.

The *portal of entrance* of staphylococci is often easily recognizable (especially in the case of wounds), and the same is true of the path of

Fig. 446.—Staphylococcus osteomyelitis of calcaneum. (Alcohol, methyl violet, carmine.) a, Trabeculæ of bone; b, bone marrow; c, purulent area; d, cocci. × 100.

the metastasis to the internal organs, whereby *inflammations of the lymph-vessels* (*lymphangitis*) and *of the blood-vessels* (*phlebitis, arteritis*) make their appearance. **Cryptogenic infections** are, however, of not infrequent occurrence, so that the first recognizable localization of the infection appears in the endocardium, myocardium, or bone-marrow. The spread of staphylococci through the blood-stream leads to multiple localization with abscess formation, and this condition is designated **pyæmia**, as in the case of the similar condition caused by the streptococcus. The combination of a staphylococcus infection with severe symptoms of intoxication is also known as **septicæmia**; and the combination of a staphylococcus pyæmia with septicæmia is also known as **septicopyæmia** (see § [illegible]).

The *Staphylococcus pyogenes aureus* is also *pathogenic for animals*: horse, dog, cattle, goat, sheep, rabbit, guinea-pig, and mouse, particularly for

the first-named, less so for the last. In these animals it causes suppuration. The staphylococcus loses its virulence easily in cultures. The inoculation of cultures of high virulence into susceptible animals causes a gelatinous œdema.

Closely related to the Staphylococcus pyogenes aureus are the **Staphylococcus pyogenes albus** (Rosenbach) and the **Staphylococcus pyogenes citreus** (Passet); these forms probably represent modified varieties of the aureus. The *albus* forms whitish, the *citreus* lemon-yellow colonies. These bacteria occur in the same regions and produce the same effects as the *aureus*, but are more rare than the last named.

The Staphylococcus pyogenes aureus usually occurs alone in the pus-foci, but not infrequently there may be associated with it other pus-cocci or even bacilli, as, for example, the Bacterium coli commune, or the typhoid-bacillus.

The **staphylococcus** forms a hæmolysin and a leukocidin (*Van der Velde*, *Neisser*, and *Wechsberg*) which destroys the leucocytes of rabbits, and also poisons which have a degenerative action upon the tissues. The bodies of dead staphylococci cause inflammation when injected into the tissues. Staphylolysin and hæmolysin and leukocidin form in the organism *antistaphylolysin* and *antileukocidin* and therefore belong to the toxins.

A serum produced by pathogenic staphylococci will agglutinate both the homologous strain as well as the majority of other pathogenic strains (*Kloppstock* and *Bockenheimer*).

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§ 155. The **Micrococcus Gonorrhœæ** or **Gonococcus** (Fig. 447) is a coccus first described by Neisser in the year 1879. It is constantly present in the discharges of the purulent catarrh, known as gonorrhœa, of the male and female urethra, and female genital canal (especially of the cervix), as well as in the secretions of gonorrhœal ophthalmia. It is regarded as the cause of gonorrhœa as well as of the blennorrhœa of the eye. Besides the specific cocci, other cocci may also be present in the gonorrhœal secretions, some of them closely resembling the gonococcus; the pus-cocci may also be present.

FIG. 447.—Gonococci in the urethral secretion from a fresh case of gonorrhœa (methylene-blue, eosin). *a*, Mucus with single cocci and diplococci; *b*, pus-cells with, *c*, pus-cells without diplococci. × 700.

The gonococcus may be cultivated upon coagulated human blood-serum, blood-serum gelatin, on human blood-serum-agar, on urine-agar; and forms on the surface of the nutrient medium a thin grayish-yellow layer having a smooth surface. It dies out easily, and grows only at higher temperatures. Wassermann recommends as culture-medium

FIG. 448.—Urethritis gonorrhoica. Cross-section through the mucous membrane which had been thrown into folds (Müller's fluid, hæmatoxylin, eosin). *a*, Normal connective tissue; *b*, *c*, inflammatory infiltrated, proliferating connective tissue of the mucosa; *d*, infiltrated and desquamating epithelium; *e*, desquamated epithelial cells and pus-corpuscles. × 100.

swines'-serum-nutrose-agar; Wertheim, 2 to 3 parts of a meat bouillon peptone-agar with 1 part of serum.

The cell of the gonococcus contains a poison (Wassermann) which, when injected into the tissues, excites inflammation.

Animals are immune against inoculations with the gonococcus. Efforts made to inoculate human beings with artificially cultivated gonococci have been successful in producing a purulent catarrh of the inoculated mucous membrane.

In the purulent secretion of the mucous membrane infected with gonorrhœa the coccus usually forms clumps, and for the greater part appears in the form of diplococci, the opposing surfaces of which are flattened (Fig. 447); but occurs also in part free (*a*), and in part inclosed within cells (*b*). It stains easily with aniline dyes, but is decolorized by Gram's method.

The gonococcus penetrates into the epithelial layer of the affected mucous membrane, and lies partly between and partly in the epithelial cells, and in leucocytes. Only the uppermost layers of the connective tissue are infiltrated. The infiltration is most marked in the case of cylindrical epithelium, while in the regions covered by squamous epithelium (fossa navicularis, vagina) the cocci lie more superficially. They cause inflammations which bear the character of *purulent catarrhs*, and are associated with a cellular infiltration of the tissue of the mucosa (Fig. 448, *b*, *c*, *d*) and with epithelial desquamation. The male and female urethra and the adjoining parts of the genital glands and ducts, and the urinary passages form the chief seats of localization. According to Scholz there occurs, after a three-weeks' duration of the disease in the male urethra, a metaplasia of cylindrical cells into stratified squamous cells, and the secretion decreases after this time. To what extent the deeper inflammations so frequently accompanying or following gonorrhœa (peri-urethral abscesses, prostatitis, epididymitis, vesiculitis, cystitis, inflammation of the ducts of Bartholin's glands, salpingitis, ovaritis, pelvic peritonitis, arthritis, etc.) are to be referred to the spread of the gonococcus or to what extent to secondary infections by the pus-cocci is yet a disputed question. According to the investigations made up to the present time there can be no doubt that the gonococcus may become widely spread over the surface of the mucous membranes. It has been many times demonstrated in the blood (Krause), in the inflamed epididymis, tubes, ovaries, joints, cardiac valves, tendon-sheaths, bursæ, in peri- and parametritic foci of inflammation, and in peri-urethral abscesses. In these cases it has been regarded as the cause of the inflammation, yet the processes which lead to suppuration, and even the metastases in distant organs, appear to be more frequently dependent upon the presence of pus-cocci.

Gonorrhœal infection is at the beginning an acute process, but may become chronic, and is cured only with great difficulty; since the gonococci can maintain themselves here and there in the urethra, tubes, etc., for years, and continue to cause inflammation.

The gonococcus produces a poison which remains essentially bound to the cell and only slightly passes over into the culture fluid. The existence of a poison producing an antitoxin has not yet been demonstrated. The best of the fluid culture-media is the one advised by Wertheim, consisting of 2 to 3 parts meat bouillon with one part of blood serum (ascitic or pleuritic fluid, etc.).

Cole and *Meakins* (*J. H. Hosp. Bull.*, 1907) obtained promising results in the treatment of gonorrhœal arthritis by bacterial inoculation. *Irons* (*Jour. Infect. Dis.*, 1908) also obtained favorable results in the similar treatment of gonococcus arthritis.

He also found that the injection of dead gonococci into individuals suffering from chronic gonococcus infections gave a "gonococcus-reaction" which may be of assistance in diagnosis.

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§ 156. **Cocci** have been demonstrated with certainty as the **cause of disease in animals** in the case of a large number of infectious diseases, and are regarded with probability as the cause in the case of others. As has already been stated, the **Streptococcus pyogenes**, the **Diplococcus pneumoniæ**, and the **Micrococcus pyogenes aureus, citreus**, and **albus** are also pathogenic for different animals, and the last-named in particular often cause spontaneous—not caused by inoculation—suppurative inflammations in animals. The disease occurring in colts and calves known as staggers, characterized by inflammations of the joints, is a staphylococcus and streptococcus infection occurring through the navel.

nd belongs to the group of septicopyæmic processes. Moreover, diseases ave also been produced experimentally in animals by different cocci hich were not pathogenic for man. Further, in many spontaneous disases of animals cocci, that are probably to be regarded as the cause, ave been demonstrated.

(1) According to *Schütz* ("Der Streptococcus der Druse der Pferde," *Arch. f. wiss. u. prakt. Thierheilk.*, xiv., 1888; *Zeit. f. Hygiene*, iii.), *Sand* and *Jensen* ("Die Aetiologie der Druse," *Deutsch. Zeit. f. Thiermed.*, xiii.), and *Poels* ("Die Mikrokokken der Druse der Pferde," *Fortschr. d. Med.*, vi.) the strangles of horses is an infectious disease, in which he mucous membrane of the upper respiratory tract is the seat of a mucopurulent nflammation, in which, moreover, the lymph-glands pertaining to the region become wollen and in part suppurate; and is caused by a *chain-forming coccus*, which can be ultivated, and, when inoculated into horses (*Schütz*) again produces the disease.

(2) According to *Schütz* ("Die Ursachen der Brustseuche des Pferdes," *Arch. f. wissensch. u. prakt. Thierheilk.*, 1887; *Virch. Arch.*, 107 Bd., 1887) the *epidemic lung-disease of horses* (infectious pneumonia) is caused by an oval *coccus*, which forms pairs and hains, and is not identical with the Diplococcus pneumoniæ (Fränkel) or the Bacillus pneumoniæ (Friedländer), and therefore not identical with the bacterium described by *Perroncito* (*Arch. ital. de biol.*, vii., 1886) as occurring in the pneumonia of horses, and held by him to be identical with the Diplococcus pneumoniæ.

(3) According to *Poels* and *Nolen* (*Fortsch. der Med.*, iv., 1886), monococci and diplococci, which in part possess a gelatinous capsule, are found constantly in the lungs and n the pleural exudate in the *contagious pleuropneumonia of cattle*. On gelatin and agaragar they form chiefly white colonies which later become cream-colored. Pure cultures njected into the lungs of rabbits, guinea-pigs, dogs, and cattle give rise to pneumonic hanges. According to *Friedberger* and *Fröhner* ("Spez. Pathologie," Stuttgart, 1896), he infective material is not known with certainty.

(4) In the *udder-inflammations* of the domestic animals, which occur sometimes sporadically, sometimes epidemically, different *micrococci* and *streptococci* have been described, and designated by various names (*Hess* and *Bergeaud*, "Contag. Euterentzündung, gelber Galt genannt," *Schweiz. Arch. f. Thierheilk.*, 30 Bd., 1888; *Frank*, "Euterentzündungen," *Dtsch. Zeit. f. Thiermed.*, ii., 1876; Kitt, "Euterentzündung," "Lehrb. d. path. anat. Diagnostik," Stuttgart, 1894; *Jensen*, "Mastitis," *Ergebn. d. allg. Path.*, iv., 1899).

(5) According to *Johne* ("Seuchenart. Cerebrospinalmeningitis d. Pferde," *Dtsch. Zeitschr. f. Thiermed.*, xxii., 1887), the cerebrospinal meningitis, which occurs epidemically in horses is caused by the *Diplococcus intracellularis meningitidis* (Weichselbaum, § 153).

(6) *Babes* found in the hæmoglobinuria of cattle, which occurs as an epidemic disease in Roumania, a coccus similar to the gonococcus, which he regards as the cause of the disease ("Sur l'hémoglobinurie bactérienne du bœuf," *Compt. rend. de l'Acad. des Sciences de Paris*, cvii., 1888; *Virch. Arch.*, 115 Bd., *Annal. de l'Institut de pathol. à Bucarest*, 1890).

(7) According to *Rivolta* and *Johne* (*Dtsch. Zeitschr. f. Thiermed.*, xii.; "Bericht über das Veterinärwesen im Königr. Sachsen f. d. J. 1885") and *Rabe* (*Dtsch. Zeitschr. f. Thiermed.*, xii.), there occurs in horses a peculiar tumor-like growth of connective tissue, designated by *Johne* as *mycofibroma* or *mycodesmoid*, which is caused by a micrococcus that grows in animal tissues in round or grape-like colonies which quickly become surrounded by a hyaline capsule, and are therefore to be reckoned as *ascococci* (*Micrococcus ascoformans*). *Bollinger* and *Glage* designate the coccus as *Botryomyces*, *Rabe* as *Micrococcus botryogenes*, *Kitt* as *Botryococcus ascoformans*. The growths consist of connective tissue, resembling those of actinomycosis, and enclose small suppurating foci of granulation tissue which contain the fungi. They appear to develop most frequently in the spermatic cord after castration, but occur also on other parts of the body, particularly in the skin (*Kitt*, "Der Micrococcus ascoformans und das Mycofibrom des Pferdes," *Cbl. f. Bakt.*, iii., 1888; *Schneidemuhl*, "Botryomycosis," *Cbl. f. Bakt.*, xxiv., 1898 [Lit.]; *Glage*: "Botryomykose." "Handb. d. pathog. Mikroorg.," iii., Jena, 1903).

(8) According to *Eberth* (*Virch. Arch.*, 80 Bd.) and *M. Wolff* (*Virch. Arch.*, 92 Bd.), many of the gray parrots brought to Europe (*Psittacus erithacus*) die of a streptococcus mycosis. The micrococci are found in almost all the organs, but especially in the capillaries of the liver and their neighborhood, where they cause necrosis of the liver-cells, but no suppuration.

(9) According to *Ostertag* ("Handb. d. pathog. Mikroorg.," ii.), the infective vaginal catarrh of cattle is caused by a streptococcus.

2. The Bacilli and the Polymorphous Bacteria, and the Pathological Processes Produced by Them.

(a) General Considerations Regarding Bacilli and the Polymorphous Bacteria.

§ 157. Under the designation **bacilli** or **bacillaceæ** (A. Fischer) or *Bacteriaceæ* (Zopf) may be classed all those bacteria which occur in the form of straight rods or rods which are slightly bent in one plane. By many authors (Cohn, Hüppe, Lehmann) the bacillaceæ are divided into two groups: **bacterium** and **bacillus**, the latter being characterized by the production of endogenous spores, while spore-formation is lacking in the former.

The **bacilli** multiply by division. The rods grow in length, and divide into approximately equal parts through the formation of a transverse partition-wall. If the division of one of the elongating bacilli is delayed, or if the separation of the individual rods from one another is not distinctly recognizable, there arise long, unbranched rods or threads (Fig. 450, *b*). If the divided rods remain attached to each other, there are formed chains of rods (Figs. 449, *c*; 450, *c*). In many forms of

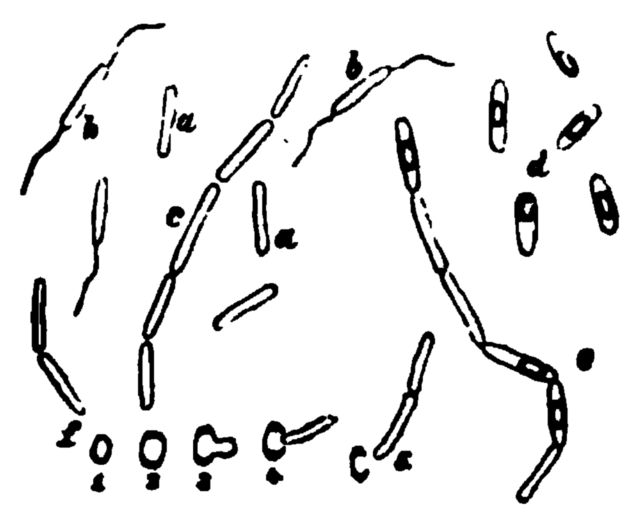

FIG. 449.

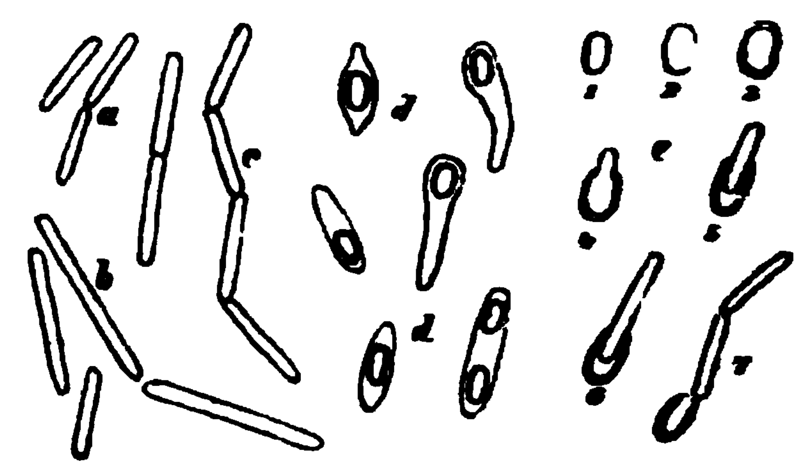

FIG. 450.

FIG. 449.—Bacillus subtilis in various stages of development (Prazmowski). *a*, Single rods; *b*, rods with flagella; *c*, chain of rods; *d*, single cells with spores; *e*, chain of rods with spores; *f* ¹—⁵, germination of a spore. × 800.

FIG. 450.—Clostridium butyricum (Prazmowski). *a*, Short rods; *b*, long rods; *c*, chain of rods; *d*, cells with spores; *e* ¹—⁷, germination of a spore. × 800.

bacilli the ends of the individual rods are blunt, in others rounded or pointed.

In many bacilli, resting as well as swarming stages are observed. Flagella serve as the organs of motion (Fig. 449, *b*); they are situated sometimes at the ends, sometimes on the sides, of the rods, and may occur in large numbers. In many bacilli an endogenous **spore-formation** is observed (Figs. 449, *d*, *e*; 450, *d*), the spores lying sometimes in the middle, sometimes at one end, of the cell. Not infrequently the spores appear within jointed threads. The germination of spores results in the formation of new rods (Figs. 449, f^{1-5}, 450 e^{1-7}).

During spore-formation the rods usually do not change their shape to any marked extent. In other cases they assume a spindle-, club-, or pear-shape (Fig. 450, *d*), and these changes have been taken as the basis for the establishment of an especial group, *clostridium*. On the other hand, numerous authors class these forms with the bacilli.

The **polymorphous bacteria** are distinguished from the bacilli by the fact that they form, besides rods, also long threads, in part with false or

true branching; and in individual cases a basal non-proliferating end and an apical proliferating end may be distinguished. In this category may be placed the fungi designated *Streptothrix*, *Cladothrix*, *Beggiatoa*, and *Crenothrix*. They are here placed with the bacilli, because, on the one hand, their botanical position is not definitely determined, while, on the other, in so far as they are pathogenic, they conform most closely to the bacilli in their biological properties (*cf.* diphtheria-bacilli, tubercle-bacilli, and actinomyces).

The **saprophytic bacilli** produce many forms of *fermentation* by their growth in nutrient fluids; many also form *pigments*. A sharp line cannot be drawn between the saprophytic bacilli and the pathogenic forms, since some saphrophytes (*Proteus vulgaris, Bacillus pyocyaneus, B. tetani, B. œdematis maligni*) occasionally develop also in the human organism. Some also form *toxins* (*B. botulinus, B. pyocyaneus*) which when taken into the organism produce intoxication.

Bacillus botulinus (Van Ermengem) is an obligate anaërobic bacillus which develops occasionally in sausage, particularly in blood and liver sausages, also in smoked meat, canned meats, game pies, salted fish, and also in preserved fruits and vegetables. The bacillus is (Van Ermengem) 4–6 μ long, 0.9–1.2 μ broad, and possesses 4–8 peripherally arranged flagella. It stains according to Gram. In the ordinary nutritive media it grows best under anaërobic conditions at a temperature of 18°–25° C., and forms endogenous spores. Acids easily inhibit its growth.

When growing in the foods mentioned above, it produces a true toxin which is very poisonous for experimental animals, and causes the formation of an antitoxin. The poison is rendered inactive by heating to 80° C., but is not changed by the digestive juices. The consumption of food in which the bacillus has already formed its toxins leads, therefore, to intoxication. On the other hand, the bacillus does not develop in the human organism, its growth being hindered by the high body temperature. The bacillus should be classed then as a *toxicogenic saprophyte*.

The disease known as botulismus or allantiasis or ichthyoismus comes on about twenty-four to thirty-six hours after the taking of the food, and is characterized essentially by nervous disturbances of central origin, secretory disturbances, motor paralysis (paralysis of accommodation, mydriasis, ptosis, and double vision), dryness and redness of the mucous membrane of mouth and pharynx, aphonia, dysphagia, etc. Constipation and retention of urine frequently take place, or there may be diarrhœa and vomiting. Death often results after a short time through bulbar paralysis.

As **Proteus vulgaris**, Hauser has described a bacillus (*Bacterium vulgare* of Lehmann) which is very frequently present in decomposing animal substances and in human cadavers, and in gangrenous ulcers, and causes putrid decomposition. It forms rods of varying length, and produces substances poisonous for animals. According to observations by numerous authors, it is not infrequently found in *human tissues*, chiefly in association with other bacteria, streptococci, pneumococci, diphtheria-bacilli; and by its presence aggravates the course of the infection and causes *putrid decomposition* of the pus and the necrotic tissue. In rare cases it may *alone*, without the association of other bacteria, *cause inflammations*, particularly of the urinary bladder (*cystitis*). Several cases of *hæmorrhagic enteritis* have also been described, in which a form of proteus was regarded as the causal agent. Further, proteus has also been found in inflammations of the female genital tract, serous membranes, and liver

(infectious icterus), and has been considered to be the cause of the given inflammation. *Proteus* must therefore be classed with the *parasitic* or *pathogenic bacteria*. Its pathogenic activity rests chiefly upon the formation of poisonous substances. (Literature given by Meyerhof, l. c.).

The **pathogenic bacilli** and **polymorphous bacteria** cause partly acute and partly chronic affections, the former terminating either in death or in healing after the destruction of the bacteria. It also happens in the acute diseases that the bacteria may remain in the body for a long time. The chronic affections are characterized by the persistence and multiplication of the bacteria within the body, so that the disease assumes a progressive character, and sometimes slowly, sometimes rapidly, new regions are in turn invaded by the bacteria and suffer pathological changes.

Bacillus subtilis is a fission-fungus whose spores are widely distributed in the ground, hay (hay-bacillus), and in the air. When cultivated upon potato or upon the dung of herbivorous animals, it forms whitish-yellow colonies; upon liquids it forms thin and thick pellicles. It requires oxygen for its development.

The fully developed rods (Fig. 449, *a*) are 6 μ long. The snake-like motions occurring at times are produced by means of numerous lateral and terminal flagella. Through the growth of the rods undivided threads are formed which after division form chains of rods. The separate cells may develop in their interior glistening, sharply contoured spores (*d*, *e*), which lie either in the middle or nearer to one end of the cell. Later the cells in which the spores have been formed die. During germination the spores become pale (Fig. 449*f*, $^{1-5}$), lose their glistening appearance and their sharp contour. A shadow then appears at each pole, while the spore begins a tremulous motion. After a time the contents of the spore project from the membrane of the spore in the form of a germinal utricle, which later becomes elongated, divides, and produces swarming rods.

The **Bacillus butyricus** (*Bacillus amylobacter* of *Van Tieghem*, *Vibrion butyrique* of *Pasteur*, *Clostridium butyricum* of *Prazmowski*) consists of rods of 3 to 10 μ in length, and also forms threads and chains of rods. During spore-formation the cells become spindle-, club-, or tadpole-shaped (Fig. 450, *d*), and then produce one to two glistening spores. In germination, after the absorption of the spore-membrane a germinal utricle appears at one of the two poles (Fig. 450, *e* $^{1-7}$); this becomes elongated, and produces new rods by segmentation.

The *Bacillus butyricus* does not need oxygen for its development; it produces butyric-acid fermentation with evolution of carbonic acid, in solutions of starch, dextrin, sugar or glycerin. In media containing starch, glycerin, or cellulose the bacilli are colored blue with iodine.

Bacillus prodigiosus grows upon potatoes and bread, as well as upon agar-agar, and upon nutrient gelatin, liquefying the latter. It forms a red coloring matter which is soluble in alcohol. The pigment is formed only in the presence of oxygen; in the growth in milk the coloring-matter is contained in the fat-droplets. The bacilli themselves are always colorless.

Bacillus fluorescens liquefaciens forms whitish cultures in gelatin, in the neighborhood of which the gelatin is liquefied, while in the remote surrounding portions it gradually takes on a greenish-yellow fluorescence.

Bacillus cyanogenes (*Neelsen*, *Hueppe*), when cultivated in sterilized milk, causes a slate-gray color that changes through the addition of acid to an intense blue. In unsterilized milk, in which lactic-acid bacteria develop at the same time, a blue color appears without the addition of acid. On potatoes it forms yellowish, slimy cultures, in the neighborhood of which the substance of the potato is colored grayish-blue (*Flügge*).

Bacillus acidi lactici ferments milk-sugar into lactic acid and coagulates casein. In gelatin it produces white cultures.

Bacillus caucasicus (*Dispora caucasica*) forms one of the constituents of the fungus-conglomerate known as kephir-ferment, which is used by the inhabitants of the Caucasus in the preparation, from cow's milk, of the alcoholic drink called kephir. The kephir-ferment consists of small granules containing yeast-cells and bacilli. The latter at times show movements, and form a round spore at the end of each rod. As the result of their growth in milk the milk-sugar is probably converted into glucose, while the yeast-cells produce alcoholic fermentation.

Bacillus pyocyaneus occurs occasionally in bandages upon suppurating wounds and causes a greenish-blue discoloration of the same. The coloring-matter called *pyocyanin* is soluble in chloroform and crystallizes from the solution in long blue needles. In addition it forms also a coloring matter soluble in water which produces a greenish fluorescence of the nutrient gelatin. (See § 163.)

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(*b*) *The Pathogenic Bacilli and Polymorphous Bacteria.*

§ 158. The **Bacillus anthracis** (*Bacteridie du charbon*) is the *cause of anthrax*, a disease occurring chiefly in cattle and sheep, and occasionally transmitted to man. It is a fission-fungus which, when inoculated into a susceptible animal, may increase within the tissues as well as in the blood.

The **anthrax-bacilli** (Fig. 451) are 3 to 10 μ long and 1 to 1.5 μ broad. In the blood of animals affected with anthrax they occur either singly or in thread-like jointed bands of two to ten rods, whose ends are for the greater part sharply cut across (Figs. 451, 452) more rarely slightly concave or even slightly convex (Johne). According to Pianese, Serafini, Günther, and Johne they possess a gelatinous capsule which is best brought out by the staining of dried preparations with methylene-blue. They can be cultivated upon blood-serum-gelatin, in bouillon, upon

slices of potatoes and [illegible], in infusions of peas and mashed grain of various kinds, etc., in the presence of oxygen; according to Klett also in an atmosphere of nitrogen, and grow most rapidly at a temperature of from 30° to 40° C. At temperatures below 15° and above 43° C. development is impossible.

Under suitable conditions of growth the rods increase in length and may within a few hours form non-segmented threads of considerable length. These consist of short segments whose outlines may be made visible by treatment with iodine or by stains (Fig. 43[illegible]). Ten hours after, the clear contents of the threads become granular, and at regular intervals there become apparent dull-shining bodies, which after a few hours enlarge into strongly refractive spores (Fig. [illegible]). Later the threads disintegrate and the spores become free.

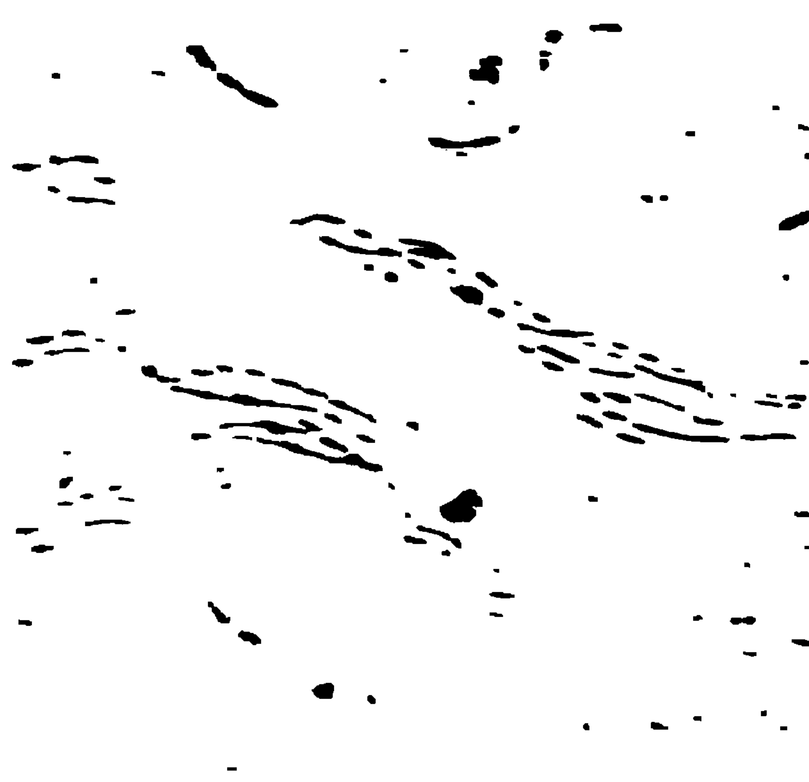

Fig. 43[illegible].—[illegible]

If the bacilli or the spores gain entrance into the blood, they increase and form rods as described above, which stain with different aniline dyes and also by Gram's method. Sections of hardened tissue show that they are present in large numbers in the capillaries (Fig. [illegible]), particularly in the spleen, liver, lungs, and kidneys. The neighbouring parenchyma for the greater part appears unchanged, still the local proliferation of the bacilli can also cause tissue-degeneration, necrosis, and hæmorrhagic inflammation. If an infection of the blood takes place during pregnancy the infection may pass over to the fœtus.

Anthrax-bacilli or their spores may gain entrance into the skin of man through small wounds, an event which is particularly likely to happen in the case of individuals who butcher, or skin, or otherwise handle the skins of animals affected with anthrax; or occasionally the infection may be transmitted by means of the sting of a fly which has taken up blood from an animal infected with anthrax. There develops at the place of infection a somewhat elevated pustule (Fig. [illegible]) from 1 mm. to several centimetres in diameter, having an arched or flattened surface, and of a red or at times a more yellowish color. This is often after a time covered with vesicles, or after the loss of the epithelium becomes moist, so that through the drying of the oozing, often bloody exudate a scab is formed (Fig. [illegible]).

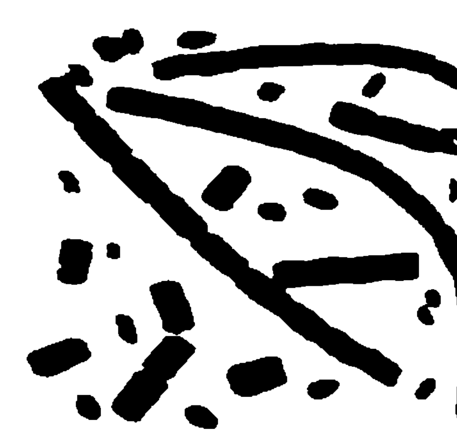

Fig. 43[illegible].—[illegible] anthrax-bacilli and free spores [illegible] the bacilli [illegible] with [illegible] × 900.

The centre may become depressed through the formation of a central scab, so that the edges form a wall about the latter. The neighbourhood of the pustule is sometimes but slightly changed, at other times reddened and swollen, and may be set with small yellow or bluish-red vesicles. If the process remains local, the gangrenous pustule may be thrown off. Infection of the blood is [illegible]. It may cause the infection from the [illegible]

beginning may show itself as an extensive, intense, œdematous swelling of the tissue without the formation of a circumscribed elevation.

In the region of a fully developed anthrax-pustule (Fig. 453), the corium (d, d_1) and the papillary body (c) are infiltrated with a serocellular

FIG. 453.—Section from an anthrax-pustule ten days old, taken from the arm of a man (alcohol, Gram's method, vesuvin). *a*, Epidermis; *b*, corium; *c*, papillary body œdematously swollen and infiltrated with exudate and bacilli; *d*, outer layer of corium, infiltrated with cells; d_1, the same, containing also bacilli; *e*, deep layers of the corium infiltrated by cords of cells; *f*, dermal tissue infiltrated with bacilli and cells; *g*, bloody exudate containing bacilli, lying upon the surface; *h*, hair-follicle; *i*, sweat-gland. × 25.

exudate as well as by bacilli. The bacilli lie particularly in the outer portions of the corium (d_1) and in the papillary body (c), but may also penetrate into the deeper layers of the corium (f). In the neighborhood of the papillary body (c) the exudate is sanguineous. Vesicles filled with bloody fluid result if the exudate extends up to the epithelial covering, and if the deeper portions of the latter become liquefied, thereby permitting the lifting-up of the superficial layers by the exuded fluid. If the upper layers of the skin are also lost, the bloody fluid containing the bacilli (g) appears upon the surface.

The cellular infiltration has its seat chiefly in the corium (d, d_1, e), and the impression is obtained as if the great massing of cells formed a certain protection against the further spread of the bacilli. The cells which collect belong for the greater part to the polynuclear leucocytes (Fig. 454). The bacilli lie sometimes in, sometimes between the cells.

If an infection with anthrax-spores takes place in the intestinal canal, an event which occurs most frequently in the small intestine, less often in the stomach and large intestine, there develop dark-red or brownish-red hæmorrhagic foci, the size of a lentil or bean or

FIG. 454.—Portion of the anthrax pustule from the arm (Fig. 453), containing bacilli. × 350.

larger, with a grayish-yellow or greenish-yellow, discolored slough in the centre. In other cases the crests of the folds of the mucosa are swollen and hæmorrhagic, and show evidences of sloughing in the most prominent parts. The mucosa and submucosa are infiltrated with blood in the region of the foci; the surrounding tissues are œdematous and hyperæmic. Bacilli are found in the tissues both in and about the foci, particularly in the blood- and lymph-vessels, and they may also be demonstrated in the neighboring lymph-glands.

Primary lung infection may also occur in man as the result of the inhalation of anthrax-spores, proving fatal in from two to seven days. Individuals who have to handle the hair of animals that have died of anthrax are especially exposed to infection; and the disease known as *wool-sorter's disease*, which occurs in men and women employed in the sorting of rags in paper-factories, is in a part of the cases nothing more than an anthrax infection. The spores taken into the lungs in the respired air develop in the bronchi (rarely in nose [Bittel]) and alveoli, in the lymph-spaces of the lungs and pleura and in the bronchial glands, and penetrate also into the vessels. Their growth causes inflammatory hæmorrhagic processes in the lungs, as well as serous hæmorrhagic exudations into the pleural cavity and the mediastinal tissue, and swellings of the lymph-glands. It may also lead to the production of necrotic foci in the lungs and in the bronchial and tracheal mucosa.

Mice, rabbits, sheep, horses, and sparrows are very susceptible to anthrax; white rats, dogs, and Algerian sheep are less susceptible or immune. Cattle are easily infected through the taking in of the spores from the alimentary canal, but are less susceptible to inoculation. Formation of spores does not take place in the tissues and in the blood.

According to *Brefeld*, *Prazmowski*, *Klein*, and others, the spore consists of a protoplasmic centre, which is enclosed by a double membrane, the exosporium and the endosporium. During germination the former is ruptured, the latter becomes the membrane of the embryo. The liberated embryo multiplies by division.

Swarming movements are not seen throughout the entire period of development; the bacilli are always motionless.

The bacilli of anthrax are easily killed by high temperatures, drying, and through the decomposition of the nutrient fluid. The spores, on the other hand, are very resistant, and are therefore usually the medium of the spread of the disease.

The colonies upon gelatin show a wavy, irregularly shaped margin, and consist of many interlacing strands of threads, which later grow out of the culture in all directions. The gelatin is liquefied immediately about the culture. On potato the bacillus forms grayish-white, slightly granular colonies having a sharply outlined border. On blood-serum it forms a white coating.

Stab-cultures in gelatin are white and during the process of growth they send out at right angles from the line of inoculation out into the gelatin, particularly near the surface. After liquefaction of the gelatin they sink to the bottom.

A marked attenuation of anthrax-bacilli may be produced by keeping the bacilli for ten minutes at a temperature of 55° C. (*Toussaint*) or for fifteen minutes at 52° C. or for twenty minutes at 50° C. (*Chauveau*), or further through the influence of oxygen under high pressure (*Chauveau*). The bacilli attenuated by exposure for a short time to high temperatures quickly regain their virulence; those attenuated at lower temperatures remain weakened for many generations.

The addition of carbolic acid to the nutrient fluid in a proportion of 1:600 permits the further development of anthrax bacilli, but destroys their virulence within twenty-nine days (*Chamberland*, *Roux*). Likewise, an attenuation may be produced by the addition of potassium bichromate (1:2,000–1:5,000). The addition of carbolic acid up to 1:500 hinders at the same time the formation of spores.

Through cultivation of the bacilli at 42–43° C. (*Toussaint*, *Pasteur*, *Koch*) their virulence may be so weakened that they no longer kill first sheep, then rabbits and guinea-pigs, and finally mice. If the temperature is kept in the neighborhood of 43° C. this result may be obtained in six days; at 42° C. it may require about thirty days.

decrease the virulence to this extent (*Koch*). By first inoculating with bacilli which kill mice but are harmless for guinea-pigs, and afterward inoculating with bacilli which kill guinea-pigs but not strong rabbits, an immunity against anthrax may be obtained in sheep and cattle but not in the case of mice, guinea-pigs, and rabbits. Such protective inoculations are, however, not of practical value, since, in order to protect against natural infection with spores from the intestinal canal, such virulent inoculation-material must be used that a large per cent. of sheep (ten to fifteen per cent.) die from the inoculations. Further, the protection afforded by the inoculations is of very short duration, and the inoculation must be repeated within a year's time.

According to observations by *Roux* and *Chamberland* anthrax bacilli which are cultivated in bouillon to which a small amount of potassium bichromate (1:2,000) or carbolic acid (1 to 2:1,000) has been added, permanently lose their power of spore-formation while retaining their virulence.

According to *Koch*, anthrax-bacilli may be cultivated in the presence of abundance of water upon potatoes and in an alkaline or neutral hay-infusion, cold infusions of pea-straw, on mashed barley and mashed wheat, in the juice of turnips, on maize, leguminous seeds, and numerous dead plants. Consequently they are able to grow and develop outside of the animal body—for example, in marshy regions and on river-banks (*R. Koch*). The entrance into the animal body is to be regarded as an accidental excursion of ectogenic bacilli. According to *Soyka* the development of spores takes place very quickly in a moist medium containing the necessary nutrient material at temperatures above 15° C. According to *Kitt* the dung of cattle forms a nutrient substratum for the bacilli.

True toxins or endotoxins have not yet been demonstrated in the case of anthrax bacilli.

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§ 159. The **Bacillus typhi abdominalis** (Fig. 455), or the *Bacterium typhi*, is a fission fungus which occurs chiefly in the form of plump rods 2 to 3 μ long, having rounded ends, and in cultures growing also in pseudo-threads. It is regarded as the cause of *typhoid fever*. When examined

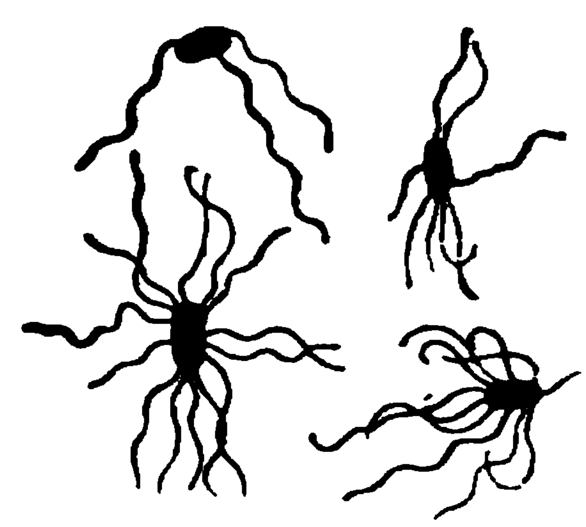

FIG. 455. FIG. 456.

FIG. 455.—Typhoid-bacilli from a pure culture. Streak-preparation (methylene-blue). × 1,000.
FIG. 456.—Typhoid-bacilli with flagella. (After Bunge.) × 1,200.

alive in cultures it shows *lively independent movements* which are accomplished by means of flagella (Fig. 456) attached to the *sides* of the rods as well as to their *ends*. The flagella may be demonstrated by proper staining-methods.

The bacilli gain entrance into the *human organism* through the drinking-water and food; though infection through the lungs is not to be excluded. According to the results of anatomical investigations, they develop particularly in the intestinal wall, in the *solitary* and *agminated follicles of the small and large intestines*, as well as in the *mesenteric lymph-glands* and in the *spleen*. In the first-named place they cause an *inflammatory infiltration of the mucosa and submucosa* (Fig. 457, a_1, b_1) which is extraordinarily rich in cells and appears in the form of flat or somewhat rounded elevations projecting above the inner surface of the intestines. An exudation of fibrin in the form of threads may take place both on the free surface and

in the deeper layers. Occasionally cellular inflammatory foci of limited extent also occur in the muscularis (c_1, d_1) and the serosa (e_1). A part of the infiltrated tissue usually sloughs and is then cast off, so that ulcers are formed. In other parts the infiltration may be absorbed and the swelling disappear.

The *swelling of the lymph-glands*, which is likewise caused by an accumulation of cells and fluid, and occasionally of fibrin, ends either in healing through the absorption of the infiltrate or may also lead to a partial necrosis of tissue. In the *spleen* the pulp in particular swells, while its vessels are greatly dilated with blood, and the parenchyma later becomes crowded full of cells and fluid.

The *bacilli are usually distributed throughout other parts of the body*, and it is probable that the inflammatory exudations in the lungs occurring at times during the course of typhoid fever are due in part to an in-

FIG. 457.—Typhoid-fever. Section through the edge of a swollen Peyer's patch (alcohol, Bismarck brown). *a*, Mucosa; *b*, submucosa; *c*, muscularis interna; *d*, muscularis externa; *e*, serosa; a_1, b_1, c_1, d_1, e_1, different layers of the intestinal wall showing infiltration; *f*, sections of glands of Lieberkühn; *g*, follicle. × 15.

crease of the bacilli within the lungs. It should always be borne in mind that aspiration-pneumonias are of very frequent occurrence in the lungs of typhoid patients, and also that *secondary infections* (cocci) may take place from the ulcers and may give rise to metastatic inflammations in different tissues. The swellings of the mucosa and submucosa and of the perichondrial tissue, which often occur in the palate, throat, and larynx, are in part the result of the specific infection, and in part of secondary disease. Moreover, typhoid-bacilli have been demonstrated in the blood, liver, gall-bladder, in the rose-spots of the skin, in the kidneys, central nervous system, testicles, in pleuritic and peritoneal fluids, in the periosteum, bone-marrow, etc., in part by means of the microscope and in part by means of cultivation. In all of these regions they may cause degeneration and inflammation, and give rise to suppuration, so that the inflammations occurring during the course of typhoid fever owe their origin sometimes to the dissemination and localization of the typhoid-bacilli, and sometimes to secondary or mixed infections. The bacilli circulate

in the blood for about two or three weeks and their cultivation from the blood may be employed as a diagnostic method. When typhoid fever occurs during pregnancy the typhoid-bacilli may pass into the fœtus.

The typhoid-bacilli produce *poisons clinging to the cells* (*typhotoxin*), and but little is known of their nature. The symptoms of the disease are for the greater part to be referred to the *intoxication*. In the course of typhoid fever there appear in the blood certain bactericidal substances which cause a degeneration of typhoid-bacilli (cf. § 31). This may be demonstrated by the fact that (Widal-Gruber reaction), through the addition of serum from an individual ill or convalescent from typhoid fever, to a bouillon-culture of freely motile typhoid-bacilli, the latter become motionless, clump together (agglutination), sink to the bottom and die. This reaction may be used as a means of diagnosis, but is not of absolute certainty, since agglutination may be produced by the serum of individuals who have not had typhoid fever, and may be absent in the case of typhoid. The agglutinating power can last for years, but it may also vanish after a month (Krause).

Individuals who have had typhoid fever may harbor the bacilli within their bodies for years after the attack, without showing any symptoms of infection ("*typhoid carriers*"). By giving off the bacilli through their urine or fæces such typhoid carriers become an element of danger to the community in which they live. ("Typhoid Bacilli Carriers." *Park, J. Amer. Med. Assoc.*, 1908.)

The **typhoid-bacillus** stains well in cover-glass preparations, with gentian-violet, alkaline methylene-blue, and Bismarck brown. It is decolorized by Gram's method. It is difficult to demonstrate it in sections of hardened tissues, since the cell-nuclei also take the stain, and because the bacilli are not uniformly distributed, but are usually found lying in the tissue in clumps.

The bacillus may be cultivated upon nutrient gelatin, agar-agar, and blood-serum, also in milk, and upon potato. Upon the last named it forms a coating which can be scarcely recognized by the naked eye; but when the surface is touched with a platinum wire it becomes apparent that it is covered with a pellicle, which on microscopic examination is shown to consist of bacilli.

On gelatin and agar-agar the bacilli form grayish-white, irregularly shaped, flat growths. *Gelatin is not liquefied.* Milk in which the bacilli are grown is not changed externally.

The cultures thrive at room-temperature as well as at body temperature. Potato-cultures made in the usual manner, when kept between 30° and 42° C., produce rods which have glistening bodies in their poles. *Gaffky* regarded these as spores, and the majority of authors formerly accepted this view. According to *Buchner* and *Pfuhl*, however, these granules at the poles are degeneration phenomena, which occur particularly when acid is present in the culture medium. The polar granules represent condensed protoplasm, and therefore stain in fresh preparations more quickly with the aniline dyes than do the other parts of the cell. The clear, colorless spots which are seen at the ends of the rods in dried and stained bacilli have been held to be identical with the polar granules and therefore regarded as spores, but are due, according to *Buchner*, to hollow spaces formed at the ends of the rods as the result of the retraction of the protoplasmic tube following the death and drying of the bacilli. Spore-formation has, therefore, not yet been demonstrated.

Cultures of typhoid-bacillus show few characteristic appearances and are with difficulty distinguished from those of other bacteria widely scattered in the outer world. Likewise their properties are very similar to those of the *Bacillus coli communis* (§ 160). Certain points of difference are as follows: The typhoid-bacilli produce no indol, while other similar bacteria, such as the *Bacillus coli*, produce it, so that bouillon cultures become red through the addition of potassium nitrite and sulphuric acid. The typhoid-bacillus produces no gas in a two-per-cent grape-sugar bouillon, while the *Bacillus coli* produces gas. Finally typhoid-bacilli in milk cause a weak acidity but no coagulation, while the *Bacillus coli* will cause at 37° C., even in twenty-four to forty-eight hours, a strong acidity and coagulation of the milk. When typhoid bacilli are grown on agar colored blue with litmus, the color remains unchanged, while *Bacillus coli* decolorizes the blue nutrient medium.

In moist earth (*Grancher, Deschamps*), in pure and impure water, typhoid-bacilli may remain alive for weeks. In artificial Seltzer water they do not die out for a

longer period (*Hochstetter*). In privy vaults and fæcal masses, or in earth saturated with fæcal matter (*Finkler, Uffelmann, Karlinski*) they may under certain conditions live for weeks and months.

Inoculations of the bacilli in the case of the animals ordinarily used for experiment do not produce a disease corresponding to typhoid fever in man. Experimental investigations show, however, that the typhoid-bacilli produce active toxins (endotoxins?) which in large doses kill the animals, causing hyperæmia and swelling of the intestinal follicles, mesenteric glands, and the spleen. Cultures injected into the tissues cause a local inflammation of greater or less intensity.

The value of the **agglutination test** is but limited, since it is hard to decide whether the agglutinating effect of the serum is brought out by the same kind of bacillus or by a related variety. In general the serum of a patient agglutinates the species causing the disease in a greater dilution than in the case of a related organism, but there occur exceptions to this rule. According to *Lubowski* and *Steinberg* the agglutinatibility of typhoid-bacilli can be easily increased in guinea-pigs and rabbits through a proteus or staphylococcus infection. Much more positive as a diagnostic method is the demonstration of typhoid-bacilli in the blood by means of cultures.

As **paratyphoid fever** there has been differentiated through observations of recent years a disease similar to ordinary typhoid fever, but which is caused by a special form of bacillus of which a type A and a type B have been described. Clinically the disease runs a lighter course than typhoid fever and rarely is fatal. The anatomical findings (*Longcope* and *Luksch*) are similar to those of typhoid fever, but the intestinal changes are less marked and ordinarily confined to the colon. It is possible to make a differential diagnosis by means of the *Widal* reaction; yet it should be noted that paratyphoid serum will agglutinate also typhoid-bacilli to a certain degree.

The **paratyphoid bacteria** stand, as far as their cultural characteristics are concerned, between the typhoid-bacillus and the Bacillus coli communis. The round, smooth-edged gelatin colonies (*Kayser*) of freshly cultivated strains do not show the superficial vein-like furrowing. In the type A they are almost colorless, while in the type B they are whitish. Both consist of short rods and are lively motile; they ferment sugar without coagulating milk; cause fluorescence in neutral-red media; grow as blue colonies on the *Drigalski-Conradi* plates and do not produce indol in bouillon cultures. Type A forms more delicate pellicles than B, and grows on potatoes in a manner similar to the bacillus of typhoid fever. Milk is not changed by type A, while it is cleared (alkaline) after several weeks by type B.

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§ 160. The **Bacillus coli communis** or the *Bacterium coli commune* (Escherich) is a fission-fungus which is constantly present in the intestinal tract of man as well as of the mammalia. The bacilli are rods 2–3 μ

long and 0.3–0.4 μ thick. They are motile and may possess as many as twenty flagella on one rod. The bacilli grow at room-temperature as well as at the temperature of the incubator. They form within the gelatin small, round, white colonies; upon its surface pellicle-like coatings. Upon potatoes they form moist coatings of the yellow color of maize or pease (Günther). They do not form spores; and are not stained by Gram's method.

The *Bacillus coli* is very similar to the typhoid bacillus, but may be differentiated from it by proper methods of cultivation and by the employment of suitable reactions (cf. § 159). It was formerly regarded as a harmless saprophyte of the colon; but from later investigations it cannot be doubted that it also possesses pathogenic properties and may cause *degenerations* and *inflammations* in various tissues. Under suitable conditions (perforation or incarceration of the intestine, or impaction of fæces) it may pass into the peritoneal cavity and excite purulent inflammations, or at least take part with other bacteria in the production of inflammation. Further, it not infrequently gains access to the bile-passages and gall-bladder, as well as to the descending urinary passages and the kidneys, giving rise to inflammations of varying intensity. The bacillus has also been found in the meningeal exudate in certain cases of sepsis; it has been demonstrated also in pericarditis, bronchopneumonia, strumitis, angina of scarlet-fever, and it cannot be doubted that it may be the cause of the affections named.

The similarity between the colon-bacillus and the typhoid-bacillus has led various authors to assume that the two bacilli are only varieties of the same species, and that the two forms may pass over into each other. At the present time the view prevails that the two bacilli are to be wholly separated from each other (§ 159). Moreover, the form of bacillus which is described as *colon-bacillus* is not a very distinct form, but represents rather a *group of different varieties.* Three to four days after the inoculation of an animal with colon-bacilli the blood-serum of the infected animal produces an agglutination of colon-bacilli (*Jatta*), which is most marked in the case of that variety which was used for the inoculation. Colon-bacillus serum (*Jatta*) agglutinates typhoid-bacilli more markedly than does normal blood-serum. On the other hand, typhoid serum can agglutinate different varieties of colon-bacilli.

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§ 161. Under the designation **Bacillus enteritidis** (Gärtner) there is placed a group of bacilli found in animals suffering with inflammations of the intestine, lungs, uterus, or udder, and with septicæmia. When gaining entrance into the human alimentary tract these bacilli excite more or less severe inflammations of the intestine characterized in part by swellings of the follicles. Man is infected by eating meat taken from animals slaughtered while in a diseased condition, and such an infection takes place most often through the meat of sick calves. Other sources of infection (drinking-water, milk, fish that have eaten diseased meat, oysters, etc.) are not excluded. The affection belongs to the group of meat-poisonings (see Bac. botulinus, § 157) occurring in different places in the form of local epidemics.

The bacilli are short, often ovoid, at times motile, and possess four to twelve flagella. They are not stained by Gram's. They form poisons that are resistant to high temperatures; and are pathogenic for mice, guinea-pigs, rabbits, calves, and apes. Injected into the tissue they cause local inflammations and give rise to hæmatogenous and lymphogenous metastases in different organs. Their entrance into the alimentary tract causes a gastro-enteritis.

The **Bacillus enteritidis** was first studied by *Gärtner* in 1888 and recognised as the cause of the gastro-intestinal form of meat-poisoning. His findings were confirmed by the investigations of *Van Ermengem, Fischer, Durham, Thomassen, Petri,* and others. The bacillus is distinguished from other bacilli such as the *Bac. typhi, Bac. coli,* etc., partly by its cultural characteristics and also by the agglutinating action of the serum of infected individuals or of previously immunized experimental animals. Surface colonies on gelatin are similar to those of the colon-bacillus. They form no indol, do not coagulate milk, but cause it to take on a yellow color; they ferment sugar with the production of gas. The infection is caused most often through the consumption of the flesh or organs of calves and cattle that have suffered from the various diseases designated as septicæmia of calves, dysentery, enteritis, pneumo-enteritis, and infectious inflammation of the intestine.

According to *Trautmann,* the bacteria of meat-poisoning and the so-called paratyphoid fever belong to the same species, to which he gives the name *Bac. paratyphosus.* The varieties of these bacilli can be differentiated only through the agglutination-test.

Meat-intoxications caused by the consumption of meat undergoing the ordinary putrid decomposition caused by bacteria (*Proteus, Bac. coli*) are very rare and are not severe. This is shown in the fact that game and cheese are often eaten in a condition of decomposition without exciting any marked gastro-intestinal disturbances or symptoms of intoxication.

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(*Bacillus Enteritidis.*)

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§ 162. The **Bacillus dysenteriæ** is a bacillus described by Shiga, Flexner, and Kruse, and is very probably the cause of severe catarrhal, diphtheritic, hæmorrhagic, and purulent inflammations of the colon that are classed with epidemic *dysentery*. Besides this form of *bacillary* dysentery there occur affections classed as dysentery that clinically and anatomically are very similar to it, but are due to other parasites, *amœbæ* in particular, or to chemically active substances (sublimate, septic poisons), or are induced by fæcal retention.

The dysentery bacillus is a plump, short rod, with rounded ends, often somewhat tapering off. They have no flagella and are non-motile. They are easily stained by aniline dyes (methylene-blue, carbol fuchsin) and often show polar staining. They are decolorized by Gram's. On the ordinary nutrient media the bacillus grows best at a temperature of 37° C., either under aërobic or anaërobic conditions.

That inflammations of the intestine similar to dysentery may be produced by bacilli was recognized by me as early as 1881 and 1882. In the Insane Asylum at Rheinau during an epidemic I found constantly the same bacillus in the wall of the thickened colon. Cultures were not made, but it is probable that it was identical with the bacillus cultivated and thoroughly studied by *Shiga* and *Kruse*.

According to the American investigators, bacillary dysentery is due to a number of types of bacilli, differing in their fermentative action, bacteriolytic and agglutination tests. In the treatment of the disease *Shiga* recommends a polyvalent serum active against all types.

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§ 163. The **Bacillus pyocyaneus** was first demonstrated in the pus of wounds in which it had produced a bluish-green discoloration. It is widely distributed throughout the outer world, being found particularly in liquid manure and dung-heaps, also in water, and also occurs in the intestinal contents of animals (swine) and of man.

The *Bacillus pyocyaneus* forms rods of varying size (0.6–1–6 μ). They possess a terminal flagellum. It is decolorized by Gram's. Spores are

not formed. It is easily cultivated upon the ordinary media and produces ferments that liquefy gelatin, coagulate milk, and break up albumin. It produces a pigment, the (in the presence of air) *bluish-green pyocyanin*, which is soluble in chloroform, and a *greenish fluorescing* pigment soluble in water but not in chloroform and which in gelatin cultures causes the greenish fluorescence of the gelatin. For the majority of experimental animals it is pathogenic, particularly for guinea-pigs and goats, and causes first local inflammation at the seat of inoculation, but later may spread through the blood. In bouillon cultures it forms both a true toxin and an endotoxin.

For man it *possesses a limited pathogenicity*. Nursing infants and children who have recently had their resistance lowered by other diseases are especially susceptible. Intestinal inflammations are most frequently to be referred to the *Bacillus pyocyaneus*, but it may cause also inflammations of the umbilicus, middle ear, localized inflammations of various organs (endocardium), and generalized infections.

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§ 164. The **Bacillus tetani** (Kitasato) is a fine, slender bacillus (Fig. 438) which is widely distributed throughout the superficial layers of the earth, and is to be regarded as the cause of tetanus. According to observations made by Nicolaier in 1885, it is often possible to produce in mice, guinea-pigs, and rabbits, by means of subcutaneous inoculation of surface-earth, a typical tetanus with fatal termination, due to this bacillus.

It was first demonstrated by Rosenbach in 1886 that this same form of bacillus is present in the seat of injury in cases of tetanus in man following trauma or freezing; and that when inoculated into guinea-pigs and mice it again produces tetanus. Since that time this discovery has been many times corroborated.

The tetanus-bacillus is anaërobic and thrives very well in an atmosphere of hydrogen, but not in carbonic-acid gas. It grows on ordinary peptone-agar that is slightly alkaline, on blood-serum, and in nutrient gelatin. The latter is liquefied with evolution of gas. The addition of from 1.5 to 2 per cent. grape-sugar to agar-agar accelerates the growth; a temperature of 36°–38° C. is most favorable for its development. It forms long, thin, bristle-shaped rods which form terminal spores (Fig. 438) giving rise to a spherical swelling at the end of the rod (knobbed bacilli). In cultures it may form long pseudothreads. The cultures give off an offensive odor; gelatin is slowly liquefied. The bacilli stain by Gram's method. They are motile except during the time of spore-

formation, and possess peritrichous flagella. Pure cultures inoculated into horses, asses, guinea-pigs, mice, rats, and rabbits cause tetanus, but in the case of rabbits larger amounts must be injected. The tetanic contractures begin in the neighborhood of the point of inoculation. Suppuration does not occur at the point of inoculation. The bacilli cannot be demonstrated after the death of the animal, and are never found in the tissues except at the seat of inoculation.

FIG. 458.—Tetanus-bacilli with terminal spores. × 1,000.

The specific action of the tetanus-bacillus is to be referred to the production of a true toxin (*tetanus toxin*) which through its haptophore group is bound to the cells of the nervous system, and thereby after a certain period of incubation excites tetanic convulsions. An antitoxin is produced in the body of man and experimental animals and by it animals may be made immune against tetanus (see § 32).

The infection—intoxication—of man takes place usually through the medium of small wounds; idiopathic or rheumatic tetanus, which does not start from demonstrable wounds, may arise through infection from the mouth-cavity and the respiratory tract (Carbone, Perrero, Thalmann). A preëxisting catarrh favors the infection (Thalmann). When taken into the alimentary tract the poison becomes inactive as the result of changes produced by the digestive juices (see § 29).

The **tetanus-bacillus** is not found isolated either in the earth or in infected wounds; and inoculations, therefore, consist of a mixture of bacteria. Attempts to isolate the bacillus by means of cultures were therefore unsuccessful with the majority of investigators. In the year 1889 *Kitasato,* in Koch's laboratory, succeeded in isolating the tetanus-bacillus by heating for a half-hour to one hour, on the water-bath, at 80° C. mixed cultures that had been kept for several days in the incubator, and then plating the cultures in an atmosphere of hydrogen. Through the heating the bacteria growing at the same time with the tetanus-bacilli were killed, while the tetanus-bacilli survived. Tetanus toxin (*Kitasato*) is destroyed by heating (65° C. and over) for a few minutes and by direct sunlight (fifteen to eighteen hours), and loses also its virulence in a few weeks under the influence of diffuse daylight.

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§ 165. The **Bacillus œdematis maligni** (*Vibrion septique* of Pasteur) is an anaërobic bacillus first carefully studied by R. Koch. It is present in various putrefying substances, and its spores are almost never absent from earth fertilized by decomposing fluids or liquid manure. The bacilli are 3–3.5 μ long, and 1–1.1 μ broad; they often form long pseudothreads. They resemble the anthrax-bacilli, though somewhat more slender, are rounded at the ends, and not sharply cut across. In spore-formation a swelling of the rod takes place, as in the case of the *Bacillus butyricus*, so that spindle- and tadpole-shaped forms arise.

The bacillus is motile, and possesses flagella on the ends as well as on the sides. It is not stained by Gram's method.

It grows in nutrient gelatin as well as in agar and coagulated blood-serum, but must be introduced deeply into the medium and protected from the air. Nutrient gelatin to which one to two per cent. of grape-sugar has been added is an especially favorable medium (Flügge). Nutrient gelatin and blood-serum are liquefied, the latter with evolution of gas.

The bacillus can be easily obtained by sewing up garden-earth under the skin of a guinea-pig, care being taken to prevent the access of air to the point of inoculation. The ensuing multiplication of the bacteria excites a progressive œdematous swelling of the subcutaneous tissue. At a later stage the bacilli spread over the serous membranes, and involve the spleen and other organs.

Mice, guinea-pigs, horses, donkeys, sheep, swine, cattle, and pigeons are susceptible to the bacilli; rabbits and fowls are less susceptible, while rats, dogs, and cats are still less so.

According to observations by Brieger, Ehrlich, Chauveau, Arloing, and others, the bacilli of malignant œdema may also occasionally develop in the human body, particularly when the tissues are poorly nourished and the bacilli through any accident—puncture of a hypodermic syringe—get into the deeper tissues. They excite gangrenous processes associated with hæmorrhagic œdema and gas-production.

As the **Bacillus phlegmones emphysematosæ** R. Fraenkel in 1892 described an anaërobic bacillus staining with Gram's which in many cases is to be regarded as the cause of phlegmonous inflammation associated with gas-formation. According to Fraenkel the bacillus is non-motile and only exceptionally forms spores. In cultures it forms gas. It occurs in the external world (by Fraenkel it was demonstrated upon a splinter of wood with which a man dying of gas-phlegmon had been

wounded); and when injected subcutaneously into guinea-pigs or sparrows produces a progressive gangrenous process with disintegration of the subcutaneous tissues and muscle, as well as free collections of fluid and gas. Intravenous injection into rabbits and guinea-pigs is followed by the formation of gas in the internal organs.

Gas-phlegmon in man occurs most frequently after severe injuries, for example, compound and complicated fractures, but may also proceed from small wounds. The bacillus is found at times in company with other bacteria, pus-cocci, colon-bacilli; at other times alone and may be present in foci in great numbers. In pure infections there occurs a production of gas associated with liquefaction of the tissue, particularly of the muscles and of the reticular connective tissue.

It is probable that this bacillus is identical with one described by Ernst, Welch, and Nuttall (by the latter as *Bacillus aërogenes capsulatus*) as the cause of "foamy liver" ("*Schaumleber*") (Ernst)—that is, with a bacillus which is regarded as the cause of gas-formation in the human liver (Ernst). The condition of "foamy organs" (*Schaumorgane*) probably arises (Fraenkel) from the fact that the bacillus in question gains an entrance before death into the tissues, into the liver in particular. Fraenkel has obtained his gas-bacillus in pure cultures from foamy organs.

Besides Fraenkel's gas-bacillus other bacteria can cause changes corresponding to those of gas-phlegmon and foamy organs, especially as the result of a localization in an already infected inflamed tissue (lactic-acid-bacilli, proteus vulgaris, and colon-bacilli).

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§ 166. The **Bacillus pneumoniæ** (**Friedländer**) is a plump, non-motile bacillus without flagella, about 0.5–1.25 μ broad and 0.6–6.0 μ long. It forms no spores (Fig. 479). It belongs to the group known as capsulated bacilli characterized by the formation of a well-defined mucous capsule. It is easily stained with aniline dyes, but is decolorized by Gram's. It grows easily on the usual nutrient media, under both aerobic and anaerobic conditions, and does not liquefy gelatin. Stab cultures in nutrient gelatin show the form of the so-called nail-culture (Fig. 480), in that the bacteria growing over the stab-canal form a white mass of bacilli similar to a nail-head.

White mice and guinea-pigs are especially susceptible to the bacillus. The first named die within sixteen to forty-eight hours after subcutaneous inoculation. The point of inoculation and the regional lymph-glands are inflamed and contain encapsulated bacilli, and the latter are found also in the blood. Rabbits are almost immune to inoculation.

Friedländer and Frobenius, who first described the bacillus (1882), believed that it was the most frequent cause of croupous pneumonia, a view that may be explained by its confusion with the, at that time unknown, *Diplococcus pneumoniæ*. It is now recognized that it is but relatively rarely the cause of this disease (according to Weichselbaum, in about six per cent of cases, according to Hom, in eight to ten per cent), but it may cause focal pneumonia, pleuritis, pericarditis, pharyngitis, rhinitis, otitis media, and meningitis. In severe infections it can also pass into the blood and set up metastases. In the inflammatory products the bacilli are found in the form of rods and short oval cells surrounded by capsules, often forming chains (Fig. 479).

Fig. 479.—Bacillus pneumoniæ (Friedländer). Encapsulated forms [illegible]

Fig. 480.—Nail-shaped stab-culture of the Friedländer pneumonia-bacillus in gelatin.

Capsulated bacilli similar to the pneumonia-bacillus are often found in the chronic inflammation of the nasal mucosa known as ozena, which is characterized by a foul-smelling secretion and the formation of scabs; and they have been demonstrated also in rhinoscleroma [illegible], and it has been assumed that they stand in causal relation to these diseases. This remains to be determined

[illegible] the fungus [illegible] is the chief representative of a group of bacilli [illegible] same *bacillus* [illegible] described [illegible]

ozæna-bacillus is identical with the pneumonia-bacillus, probably also the bacillus from the milk-fæces of nurslings described as the *Bacterium lactis aërogenes* (*Escherich*). It is possible that a greater etiological significance may be attached to it in so far as the origin of many diarrhœas is concerned.

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§ 167. As the **influenza-bacillus** (Fig. 461) there was described by R. Pfeiffer, in the year 1892, a bacillus whose occurrence in influenza has been many times confirmed; it is now regarded as the cause of influenza. In individuals suffering from influenza it is found in the catarrhally affected respiratory passages, occasionally also in the lungs; and the small bronchi may contain enormous numbers of the bacilli in pure culture. It is assumed that their multiplication in the respiratory tract gives rise to the inflammation, and that the bacilli produce poisons, which, when absorbed, cause the symptoms characteristic of influenza. The bacilli may also pass into the blood and become spread throughout the body. The inflammatory changes of internal organs occurring during influenza are to be referred in part to the influenza-bacillus, in part to the poisons produced by them, and in part to secondary infections.

The influenza-bacilli are very small, thin rods with rounded ends (Fig. 461), which lie separate or joined together in twos. They stain with the ordinary aniline dyes, but not by Gram's method. They may be cultivated at the body-temperature upon blood-agar or upon agar that has been smeared with human or pigeon blood or to which milk has been added. They form upon this medium small, drop-like colonies as clear as water. According to Ghon and v. Preiss, the nutrient medium must contain albumin. Spore-formation has not been observed. In apes a catarrhal inflammation of the respiratory tract may be produced by intratracheal injections of pure cultures. Rabbits may be poisoned through the incorporation into their bodies of cultures; and are affected in consequence by a paralytic weakening of the muscles and dyspnœa. According to Cantani, the poison produced by the bacilli exerts its effects particularly upon the central nervous system.

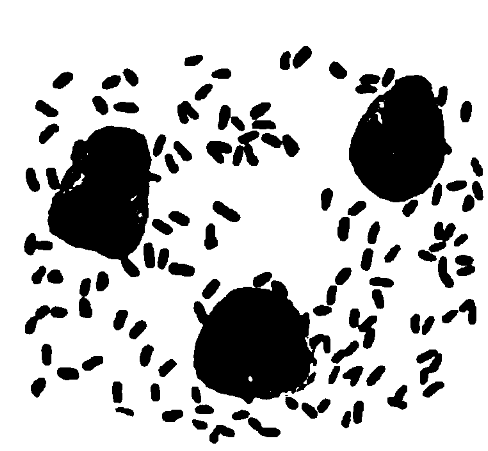

Fig. 461.— Influenza-bacilli and pus-corpuscles, from sputum (fuchsin). × 1,000.

According to investigations by *Czaplewski* and *Hensel* ("Bakteriolog. Untersuch. über Keuchhusten," *Centrbl. f. Bakt.*, xxii., 1897) and *Koplik* ("Die Bakteriologie des Keuchhustens," *Centralbl. f. Bakt.*, xxii., 1897), there is found in the respiratory tract in **whooping-cough** a small, non-motile **bacillus** similar to the influenza-bacillus, which is thought to be the cause of whooping-cough. *Luzzatto* ("Zur Aetiol. des Keuchhustens," *Centralbl. f. Bakt.*, xxvii., 1900) found in cases of whooping-cough two bacilli, but was unable to determine with certainty their pathogenic significance. *Jochmann* and *Krause* ("Aetiol. des Keuchhustens," *Zeit. f. Hyg.*, 36 Bd., 1901; Bd. 44, 1903) found in whooping-cough a bacillus resembling the influenza-bacillus (*Bacillus pertussis, Eppendorf*); this could be cultivated upon media containing hæmoglobin; they regard it as the cause of whooping-cough. Their bacillus is not identical with the one described by *Czaplewski* and *Hensel*, and later also by *Reyher* (*Jahrb. f. Kinderheilk.*, 58 Bd., 1903).

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§ 168. The **Bacillus diphtheriæ** (Fig. 462) was first thoroughly studied by Löffler; it is found in the croupous membrane occurring in diphtheria, and is regarded as the cause of this disease. In the internal organs, as the spleen and lymph-glands, it is either entirely absent or present in such slight numbers that it can be demonstrated only by methods of cultivation.

The bacilli are 1.5–3 μ long, and are often somewhat swollen at the ends. In cultures they form rods of varying length (Fig. 462), the ends of which are often clubbed or pointed. When stained the bacilli appear spotted or granular. They stain best in a staining-solution composed of 30 c.c. of concentrated alcoholic methylene-blue solution in 100 c.c. of 0.0001 per cent. potassium hydroxide solution, after which the sections are treated for a few seconds in a 0.5-per-cent. solution of acetic acid and then with alcohol. In stained preparations the bacilli often appear segmented. They also stain by Gram's method, provided the treatment with Lugol's solution and alcohol is of brief duration.

Diphtheria-bacilli grow best in the presence of air (Löffler) on a mixture of three parts of calf's or sheep's serum, and one part of neutralized veal-bouillon, to which one per cent. of peptone, one per cent. of grape-

sugar, and 0.5 per cent. of common salt are added; or upon blood-serum and agar-agar with an addition of ten per cent. glycerin or of sugar-containing bouillon (Kolisko, Paltauf, Kitasato). They form grayish-white colonies. For their development they need a temperature above 20° C.; they grow best at 33°–37° C. They are resistant to drying; but may be quickly killed by moist heat. Spore-formation has not been observed.

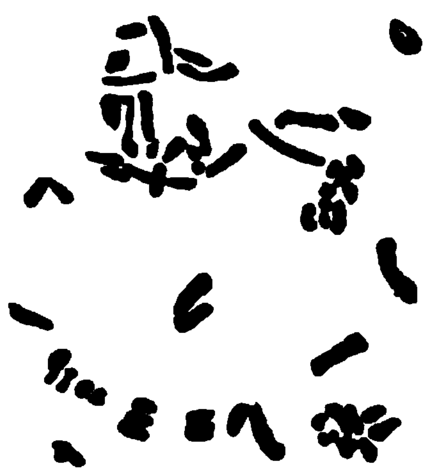

FIG. 402.—Diphtheria-bacilli from a pure culture. Streak-preparation (methylene-blue). × 1,000.

Guinea-pigs inoculated subcutaneously with cultures of diphtheria-bacilli die in two to three days (Löffler, Roux, Yersin); whitish deposits and a hæmorrhagic œdema are found at the point of the inoculation. The inoculation-area contains bacilli, the internal organs, on the contrary, are free. The *introduction of cultures into the opened trachea* of rabbits, chickens, and pigeons, as well as the *inoculation of the conjunctiva of rabbits* and the *vagina of guinea-pigs* is followed by an inflammation with the formation of a pseudomembrane. Sheep, horses, cats, dogs, cows, rabbits, and pigeons are susceptible to subcutaneous inoculation. Rats and white mice are nearly immune.

Roux, Yersin, Löffler, Spronck, and others observed the later appearance of paralysis in pigeons and guinea-pigs surviving the inoculation. Roux and Yersin assert that the intravenous injection of filtered bouillon-cultures free from bacteria will cause in guinea-pigs and rabbits after two to three days a severe illness characterized by paralysis and fatal termination.

The virulence of the cultures varies greatly. Diphtheria bacilli produce in the human body and also in cultures **toxins**, which may be precipitated by alcohol and obtained as a whitish powder.

Water-solutions of the poison injected subcutaneously into animals cause local tissue-necrosis, hæmorrhagic œdema, and inflammation; when taken up into the body-juices they give rise to pleural effusions, nephritis, fatty degeneration of the liver, and paralysis.

Diphtheria in man is characterized by an inflammation involving usually the mucous membrane of the pharynx, palate, arch of the palate, and upper respiratory passages. It appears as a *febrile infectious disease associated with symptoms of intoxication* and gives rise to local *croupous exudations*, in part also to diphtheritic sloughings (cf. § 91, Figs. 199, 200). The croupous membranes constitute the most striking feature of the disease; they are found in the throat and nose usually in the form of circumscribed flat patches, more rarely uniformly spread over larger areas; or, on the other hand, they may form a continuous layer lining the larynx and trachea, or even the bronchi. Beneath the croupous membrane the epithelium is for the greater part lost; and the connective tissue of the mucosa is hyperæmic, infiltrated, and swollen (Fig. 199). In severe cases the superficial layers of the connective tissue are necrotic in places, most frequently in the tonsils, which are more or less, often markedly, swollen. Of the deeper tissues the neighboring cervical *lymph-glands* in particular are swollen, and often show, when examined microscopically, small foci of necrosis and degeneration. Of the internal organs the kidneys especially are accustomed to show changes, in the form of a more or less severe fatty degeneration of the epithelium and of the cells of the capillary walls; not infrequently they also present swellings and focal areas of small-celled infiltration. In the spleen

there are frequently found areas of degeneration in the white-appearing follicles, in which the cells are more or less necrosed, in part disintegrated and have lost their nuclei. In the blood many of the leucocytes show fatty degeneration. Degenerative changes and areas of inflammation are not infrequently found in the heart-muscle. Paralyses are caused by degeneration and necrosis (Katz) of the ganglion-cells of the medulla oblongata and of the spinal cord and of the corresponding nerves.

The lungs are not demonstrably changed by the diphtheria poison, but bronchopneumonia, due to the aspiration of irritating bronchial contents or to an extension of the bronchial inflammation to the respiratory parenchyma, is of frequent occurrence.

The *local inflammations of the mucous membranes* as well as the *symptoms of intoxication may be caused by the diphtheria bacilli and their toxins alone*; but it must be noted that *streptococci* are almost regularly present in the diseased area, and that a *pure streptococcus infection* may present the clinical and anatomical picture of a "*diphtheria*." When both bacteria are present the injurious effect of one may be supplemented by that of the other, and the presence of streptococci appears to increase the virulence of the bacilli. In severe forms of diphtheria streptococci are usually present in great numbers; yet every streptococcus infection does not warrant a bad prognosis, since the virulence of the cocci varies greatly.

In the course of the infection with diphtheria bacilli there arise in the body *antitoxins*, which nullify the poisonous action of the toxins, and aid and make possible recovery from the disease. The formation of antitoxins follows the inoculation of animals with attenuated bacilli, and upon this rests the possibility of obtaining from animals (sheep, horses), that have been repeatedly inoculated with bacilli of increasing virulence, a serum which contains an antitoxin of value for therapeutic purposes (cf. § 32).

Lehmann and *Neumann* call the diphtheria-bacillus *corynebacterium* on account of the club-shaped appearance of the rods. Since the bacilli can also form *branching threads* in cultures, they class it with the *hyphomycetes*, among which the tubercle-bacillus and the fungus of actinomyces (oöspora) are also classed by them and others.

Ehrlich distinguishes different kinds of poisons produced by the diphtheria-bacillus, namely, *toxins* and *toxons*, these again representing no bodies of definite unity, but breaking up into several subdivisions (prototoxin, deuterotoxin, and tritotoxin) which are distinguished by the different degrees of avidity with which they unite with the antitoxin. The toxin produces the typical picture of the disease, while the toxon causes the after-symptoms, marasmus and pareses. The toxon shows a less affinity for the antitoxin.

As a lethal dose of the diphtheria poison *Ehrlich* designates that amount of the poison which is sufficient to kill in 4-5 days a guinea-pig weighing 250 gm. As a normal poison *von Behring* designates a solution of the poison which contains one hundred lethal doses per c.c. *A simple healing serum or a unit of the antitoxin*, that is, *one immunity unit* (I.-E.) is one, 1 c.c. of which will neutralize 1 c.c. of the normal poison.

According to *Löffler*, *von Hoffmann*, *Roux*, *Yersin*, *Babes*, and others there are very frequently present in the mouth and throat bacilli, which are often designated **pseudo-diphtheria bacilli**. These resemble the true bacilli of diphtheria and can be distinguished from them only in cultures. Since the diphtheria-bacilli can lose their virulence, it is not impossible (*Roux*, *Yersin*) that both bacilli represent varieties of the same species. *Lewandowsky* distinguishes four forms as belonging to the group of corynebacteria: *Corynebacterium commune* (*B. pseudo-diphthericum*), *C. diphtheriæ*, *C. conjunctivæ* (*B. xerosis*), *C. pyogenes*.

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See also § 32.

§ 169. The **bacillus of bubonic plague** (**Bacillus pestis**) was discovered in 1894 by Kitasato and Yersin, of the Japanese and French commission, while investigating an epidemic which had broken out in Hong-Kong. The pest-bacillus is a small rod with rounded ends (resembling the bacillus of chicken-cholera). It stains easily with aniline dyes, especially well with methylene-blue, and in part shows an exquisite polar staining (Fig. 463). It is decolorized by Gram's method. It is found in all cases of plague, in especial abundance in the swollen lymph-glands, but also in the spleen and blood. It may be cultivated upon the various media, and forms bluish-gray colonies, which contain rods of various lengths. It multiplies abundantly in bouillon containing sugar, and forms toxins. Independent movements have not been observed. Spores are not formed. The bacilli are easily killed by warming, but are able to withstand drying well.

The *bubonic plague*, which destroyed great numbers of the inhabitants of Europe, at the close of the seventeenth and beginning of the eighteenth centuries ("Black Death"), has since 1720 almost disappeared from Europe and has shown itself only here and there in Eastern Europe. In different countries of Asia (Yunnan in China, Arabia, Mesopotamia), and in the interior of Africa (Koch) the disease seems to be endemic, and spreads from time to time in the same manner as cholera.

Man is infected usually through the skin, more rarely from the mucous membrane of the mouth, nose, throat, and conjunctiva, still more rarely from the deeper parts of the respiratory tract, although cases of primary pest-bronchitis and pest-pneumonia occur. Small wounds usually form the avenue of entrance in the skin, but it appears (Albrecht and Ghon) that a violent rubbing of an area of the skin with infected fingers or clothing may be sufficient to bring about an infection.

The bacilli are taken up by the lymph-vessels and taken to the regional *lymph-glands*, where they cause a very marked swelling of the infected gland or group of glands—the *primary bubo*. Through the infection of lymph-glands situated farther along the lymph-system there arise *primary buboes of the second class*, and by metastasis through the blood-stream *secondary buboes* are formed. The plague is thus characterized in the first place by an *acute polyadenitis*. Since the poisons which are in association with the bodies of the pest-bacilli exert a degenerative and necrotic effect upon the vessel-walls, numerous *hæmorrhages* are also caused, and these are absent only in rare cases. To these changes there are also added circumscribed foci in the spleen, liver, kidneys, lungs, skin, etc. With the exception, therefore, of those cases

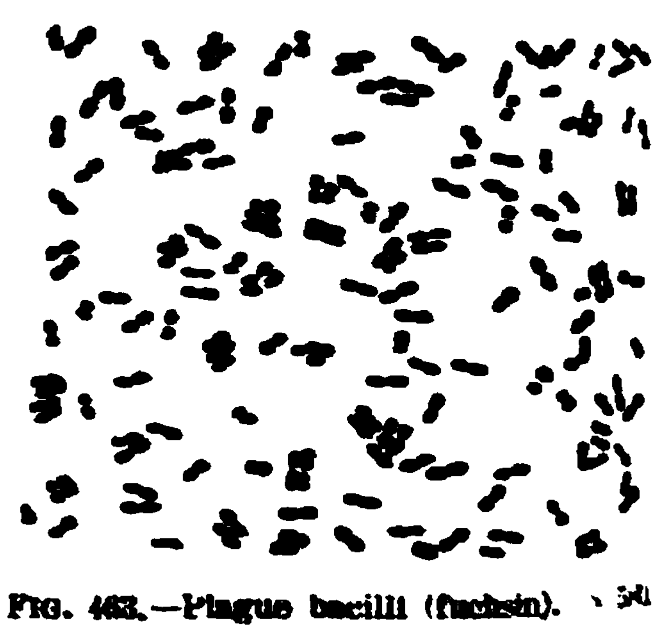

Fig. 463.—Plague bacilli (fuchsin). × 500.

in which the pest-infection is confined to the primary bubo, the disease is to be regarded as a *general infection* (Albrecht and Ghon), which arises from the taking-up of bacteria from a primary focus of infection, and runs its course with the clinical picture of a *polyadenitis* and a severe *hæmorrhagic septicæmia*.

The individual foci are characterized by tissue-necroses of the nature of *coagulation-necrosis* (Albrecht and Ghon), as well as by *severe exudations, inflammation*, and *hæmorrhage*, and are caused by the presence of extraordinarily large numbers of bacilli. The lymph-glands of the primary bubo show either wholly or for the chief part the appearance of hæmorrhagic infarction, and are swollen and of a medullary consistence. After the course of a few days they also show yellow necrotic areas which later undergo liquefaction. When the disease has lasted longer than six days, the liquefaction of the lymph-glands may take on the character of a *suppuration*.

The tissues in the neighborhood of the lymph-gland are always more or less œdematously swollen, infiltrated with blood; and hæmorrhages are also found in the walls of the neighboring large veins.

The secondary inflammations of the lymph-glands and of the lymph-adenoid tissue of the mouth and throat do not usually cause such a marked degree of swelling as do the primary; they resemble the medullary swelling occurring in typhoid fever. The surrounding tissues are also less changed, but if the process be prolonged the picture comes to resemble that of the primary buboes.

The spleen of plague-patients is somewhat swollen, dark red, finely granular, shagreened (Albrecht and Ghon), and often contains small necrotic foci, which are caused by the development of the bacilli in great numbers.

In the glandular organs and in the skin, there occur, besides hæmorrhages, also necrotic areas and exudative inflammations, all due to the presence of bacilli. In the lungs there may occur, in addition to the primary pest-bronchopneumonia, secondary metastatic focal inflammations and aspiration-bronchopneumonias.

The majority of individuals infected with pest die within the first eight days, but others may live several weeks and then die of marasmus.

Not infrequently *secondary infections*, particularly of streptococci and diplococci, are associated with the pest-infection. They arise chiefly in the tonsils and follicular glands of the tongue following the changes caused by the pest-bacilli (Albrecht and Ghon).

Among *animals, rats, mice, apes*, and *cats are especially susceptible to pest;* and in these, particularly in rats, spontaneous infections occur, so that they may aid in the spread of epidemics. Swine and dogs are less susceptible, birds still less so.

The changes in infected animals agree in general with those observed in man. The infection may remain local or become general. After the lymphadenitis and the multiple hæmorrhages there arise also miliary, tubercle-like foci in the spleen, liver, and lungs. The course is usually acute, rarely chronic. In the latter case the larger necrotic foci may be encapsulated by connective tissue. The animals are easily infected from the skin, as well as from the mucous membranes of the intestinal and respiratory tracts; and such infection may take place from an uninjured mucous membrane. The inoculation of one mouse confined in a cage with other mice may give rise to a cage-epidemic (Schottelius).

Attempts to *immunize animals and man against pest by means of dead and attenuated pest-bacilli* have been many times carried out, especially by *Yersin*, *Haffkin*, and *Lustig*; and have been successful in so far that rodents, horses, and apes have been rendered immune against inoculations otherwise fatal. According to the reports of such attempts in man, a smaller per cent. of inoculated individuals acquire the disease than of those not inoculated; but doubt is thrown upon the results of these inoculations by other authors (*Bitter*). Further, *attempts at immunization and healing have been made in man, with the serum of animals which have been rendered immune*, particularly of horses (*Yersin*, *Lustig*); and different authors ascribe to such serum a favorable influence.

Sticker differentiates the following forms of pest according to the first localization of the bacilli: (1) Bubonic plague (the most common form); (2) the cutaneous form (formation of vesicles and ulcers or furuncle-like inflammations); (3) the pulmonary form; (4) the intestinal form.

Through the investigations of *Ducrey*, *Krefting*, and *Petersen* (cf. *Petersen*, "Ulcus Molle," *Arch. f. Derm.*, xxix., 1894; xxx., 1895, and *Babes*, "Handbuch d. pathog. Mikroorg.," iii., 1903) it is probable that the *ulcus molle* or *soft chancre* is caused by a bacillus. *Tomasczewski* ("Der Erreger des Ulcus," *Z. f. Hyg.*, 42 Bd., 1903) has demonstrated through self-inoculation that a typical ulcus molle can be produced with cultures grown upon blood-agar or blood. The bacillus is non-motile, does not stain with Gram's, and often forms chains. (See also "Observations on the Distribution and Culture of the Chancroid Bacillus," by *Davis*, *Jour. of Med. Res.*, 1902).

Some years ago *Sanarelli* ("Sur la fièvre jaune," *Ann. de l'Inst. Pasteur*, 1897; *Cent. f. Bakt.*, xii.) described as the cause of **yellow fever** a bacillus whose properties he sought to determine by means of culture-experiments and animal-inoculations. He is still of the opinion that his *Bacillus icteroides* is the cause of yellow fever ("Zur Lehre vom gelben Fieber," *Cbl. f. Bakt.*, xxvii., 1900), and reports favorably of the protective and curative effects ("Expér. sur l'emploi du sérum curatif et préventif de la fièvre jaune," *Ann. de l'Inst. Pasteur*, 1898) of his serum obtained from vaccinated animals (dogs, horses, cattle). *Freire* ("Man. sur la bactériologie, pathogénie et traitement de la fièvre jaune," Rio de Janeiro, 1898, *Cbl. f. Bakt.*, xxvi.) on the other hand opposes energetically the correctness of Sanarelli's views, and maintains that the cause of yellow fever is a coccus earlier described by him, which he calls the *Micrococcus xanthogenicus*. *Bandi* ("Aetiologie und Pathogenese des gelben Fiebers," *Z. f. Hyg.*, 46 Bd., 1904) favors the pathogenic significance of the Sanarelli bacillus. It is very probable that neither Sanarelli's bacillus nor the coccus described by Freire has any etiological relationship to yellow fever. It is much more likely that the cause will be found among the protozoa, since the pathogenesis corresponds more to that of malaria and infection with trypanosomes. (See these.) Other writers (*Novy*) suggest that the etiological agent of yellow fever may be found to belong to the spirilla.

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§ 170. The **Bacillus tuberculosis** is the cause of the infectious disease occurring so frequently in man and the domestic animals which is known ordinarily as **tuberculosis**, but is also sometimes called *pearl disease* (*Perlsucht*) in animals.

The tubercle-bacillus was discovered and thoroughly studied by Koch in 1882. It is a slender rod (Fig. 464). of 1.5–4 μ in length, and is usually slightly curved. It may be stained by aniline-dyes (fuchsin, gentian-violet) to an aqueous solution of which an alkali, or carbolic acid, or aniline oil is added. The bacilli when once stained retain the stain, even when the preparation is decolorized in dilute sulphuric acid, or nitric acid, or hydrochloric acid and alcohol.

The stained bacilli not infrequently show in their interior clear, shining, unstained areas, or are composed of little stained spherules. Koch formerly regarded these clear spots as spores, and this view was generally accepted for a long time. Nevertheless, a germination of these structures could not be demonstrated, and at the present time they are no longer regarded as spores. Consequently, the tubercle-bacilli form no special resistant forms, but on the other hand the bacilli are more resistant against external influences, for example, against drying, than are many other bacteria.

The tubercle-bacilli may be cultivated at the body temperature and in the presence of oxygen upon coagulated blood-serum, blood-serum-gelatin, nutrient agar, and in bouillon. They increase, however, very slowly, so that only on the seventh to tenth day or even later, do the cultures become visible in the form of dull-white flakes resembling little scales. Larger cultures form, on the surface of coagulated blood-serum, whitish, irregularly shaped, lustreless deposits. According to Nocard, Roux, and Bischoff the growth of the bacilli is greatly aided by the addition of glycerin (four to eight per cent). In cultures the tubercle-bacilli also form threads, which in part show branching.

FIG. 464.—Tubercle-bacilli. Sputum from a man suffering with pulmonary tuberculosis. Smear-preparation on cover-glass, stained with fuchsin and methylene-blue. × 400.

At temperatures below 28° C. and above 42° C. the growth of the bacilli ceases. Sunlight kills the bacilli in a short time (Koch).

If the bacilli from pure cultures are inoculated into experimental animals, tuberculosis is produced in these; and the infection is transmitted as well by inoculation under the skin, or into the peritoneal cavity, or the anterior chamber of the eye, as also by inhalation of an atomized suspension of the culture, by feeding, and by injection of bacilli into the veins. In experimental feeding success is often attained only after long administration of the

bacilli, since not every bacillus gaining entrance into the intestinal tract leads to infection. It is also true that bacilli lodging upon the mucous membrane of the respiratory tract do not always succeed in growing in the tissue. Guinea-pigs, rabbits, cats, and gray field mice are especially susceptible; dogs, rats, and white mice less so.

Infection of man and of animals occurs from the taking up of tubercle-bacilli from the lungs, respiratory passages, and the intestinal tract, or from wounds and tissue-ulcerations. In the alimentary tract the lymphadenoid apparatus, tonsils, and the intestinal lymph-follicles form the most frequent avenue of entrance. Nurslings are particularly susceptible to intestinal infection. Further, a direct transmission of the bacilli from the mother to the *fœtus in utero* may occur, but this is rare. A multiplication of the bacilli, that is, the production of tuberculosis, occurs usually at the points of entrance of the bacilli, but may also occur only after the transportation of the bacilli through the blood or lymph, so that hæmatogenous or lymphogenous disease of the internal organs, for example, of the lymph-glands, bones, brain, and tubes, may occur as the primary localization.

FIG. 465.—Tubercle from a fungous granulation of bone (Müller's fluid, Bismarck brown). *a*, Giant-cell; *b*, epithelioid cells; *c*, lymphoid cells. × 400.

The bacilli are spread throughout the external world chiefly by the

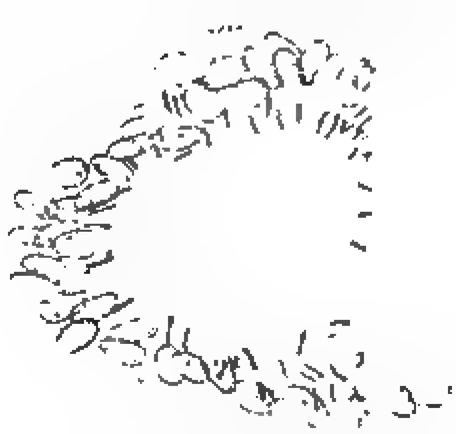

FIG. 466.—Giant-cell containing bacilli, and showing necrotic centre, from a tubercle. Stained with gentian-violet and vesuvin, mounted in Canada balsam. × 350.

sputa, under certain conditions also by the fæces and urine, further from tuberculous ulcers, or from tuberculous organs which are taken from living or dead persons. Since the bacilli are rather resistant, they may be preserved outside of the animal body for a long time under certain conditions, and may become mixed with the respired air, as well as with

the food and drink. The milk of tuberculous cows contains the bacilli especially when the udder is diseased; but the bacilli may also pass into

Fig. 467.—Tuberculosis of the pleura (alcohol, Van Gieson's). *a*, Thickened and proliferating pleura; *b*, tubercle with giant-cells; *c*, deposit of fibrin. × 300.

the milk when no disease of the udder can be demonstrated (Hirschberg, Ernst, Leuch).

If the bacilli succeed in developing and multiplying in any tissue of the human body, they lead by a series of changes to the formation of

Fig. 468.—Large-celled tubercle containing fibrin, from a tuberculous lung (alcohol, fibrin-stain). *a*, Fibrin; *b*, giant-cell; *c*, large-celled tissue. × 300.

nodular masses of granulation tissue or **tubercles**, which remain devoid of *blood-vessels*, and after reaching a certain stage of development undergo

retrogressive changes. The formation of the nodule may be accompanied by a more or less extensive inflammatory exudation.

The first effect of the development of the bacilli in a tissue is a *tissue-degeneration*, in which the tissue-cells as well as the connective-tissue ground-substance over a larger or smaller area are destroyed. To the degenerative processes there is added then on the one hand an inflammatory exudation—that is, *emigration of leucocytes and lymphocytes*—and, on the other hand, a *proliferation of the tissue-cells remaining preserved* within the affected area (Fig. 465, *a*). The degree of the exudative processes in the region of the nodule varies and is dependent upon the number and the virulence of the bacilli present in the tissue and also upon the mode of infection. When a large number of bacilli are introduced into the lung through the respiratory tract the exudative inflammation is very pronounced. It is less marked in the case of the introduction of bacilli into the liver through the portal vein.

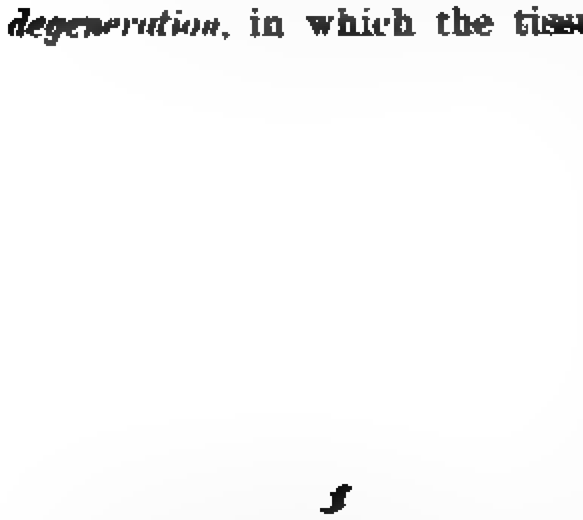

FIG. 469.—Caseous necrosis of tuberculous granulation tissue (alcohol, fuchsin, aniline blue). *a*, Granular, a_1, lumpy caseous masses; *b*, fibrocellular tissue; *c*, giant-cell with bacilli; *d*, bacilli in cellular tissue; *e*, bacilli in necrotic tissue; *f*, bacilli enclosed in cells. × 200.

The *cells of the exudate* first appearing are chiefly *polynuclear leucocytes*, but later *mononuclear lymphocytes and leucocytes* predominate. The *appearances* of *proliferation* may be shown by the second day.

The *cellular nodule* which after the course of a few days represents the

FIG. 470. Section of miliary tubercle of the omentum (alcohol, hæmatoxylin, eosin). *a*, Caseous centre containing remains of fat-cells; *b*, fibrocellular periphery; *c*, giant-cells; *d*, fat tissue. × 100.

tubercle at the height of its development shows usually three types of cells—*large epithelioid cells, with clear nuclei* (Fig. 465, *b*), *multinuclear giant-cells* (*a*), and *lymphocytes* (*c*). The first two forms are found particu-

larly in the central part of the tubercle, the latter at the periphery. The number of the individual cell-forms varies, and under certain conditions the lymphocytes may be so numerous as greatly to overshadow the larger

FIG. 471.—Fibrocaseous tubercle of the lung (alcohol, Van Gieson's). *a*, Caseous centre; *b*, thick, homogeneous connective tissue poor in nuclei; *c*, connective tissue rich in cells; *d*, lung tissue. × 80.

cell-forms. On the other hand, at other times the epithelioid cells with lightly staining nuclei may predominate. These cells are in part changed

FIG. 472.—Fibrous tubercle in the thickened synovial membrane of the knee-joint (alcohol, hæmatoxylin, picric acid, fuchsin). *a*, Connective tissue; *b*, *c*, *d*, fibrous tubercle. × 75.

lymphocytes arising from the blood (polyblasts); in part fibroblasts arising through the proliferation of connective-tissue cells *in loco*.

The giant-cells belong usually to the syncytial type and arise through

the confluence of cells, but it is also possible that they arise through the multiplication of the nuclei in a single cell. The nuclei lie usually in the peripheral portion of the protoplasmic mass (Figs. 465, *a*, and 466); sometimes collected at one pole, sometimes at both poles; sometimes arranged in a wreath or in a crescent. They often contain numerous bacilli (Figs. 466 and 469, *c*). The non-nucleated portion of the protoplasm may often be recognized to be changed, degenerated, or necrotic because of its reaction toward stains (Fig. 466).

Through the proliferation of the cells the remaining connective-tissue stroma of the original tissue is pushed farther and farther apart, so that the individual cells come finally to be separated from one another only by scanty fibres, whose general arrangement is in the form of a network, which is consequently called the *reticulum of the tubercle*.

New vessels are not formed within the tubercle; and the *old vessels are closed through the proliferation of the vessel-walls*. Usually the *new-formation of connective tissue stops with the production of fibroblasts.*

The neighborhood of the tubercle proper may show no essential change, but usually presents the appearance of an inflammation, particularly a small-celled tissue infiltration or proliferation (Fig. 467, *a*).

A serous exudation is also usually associated with the cellular emigration, and *fibrin* may be formed both *within the tubercle itself* (Fig. 468, *a*) and *in its neighborhood* (Fig. 467, *c*).

At the height of its development the tubercle forms a small, *gray, translucent cellular nodule,* which may reach the size of a millet-seed, and encloses in its tissue tubercle-bacilli in larger or smaller numbers. When it has reached a certain size *retrogressive changes* usually appear in its centre, the tubercle in consequence becoming cloudy, opaque, and of a white or *grayish-white* or *yellowish-white color*—these changes being designated as caseation.

The caseation of the tubercle is dependent on the one hand upon a *necrobiosis of the cells,* and on the other upon the *deposit of coagulated substances* in the spaces between the cells. The cell-necrosis is characterized by a loss of the nuclei and a transformation of the cells into lumpy masses which later disintegrate and become granular (Fig. 469, *a*, *a*). The deposit between the cells consists either of a network of fibrin (Fig. 468, *a*) or of a granular or hyaline reticulated fibrinoid substance resembling fibrin but which does not take the Weigert's fibrin stain and is stained yellow by Van Gieson's. In the further course of the process of caseation the fibrin and fibrinoid substance disintegrate into a granular mass which fuses with the cell-detritus, so that the central part of the tubercle consists of a lumpy granular mass (Figs. 469, *a*, 471, *a*) which takes a weak diffuse stain with nuclear stains.

The caseation affects at first the central portion of the tubercle, and is usually confined to this, while connective tissue is formed at the periphery, so that the *tubercle* comes to consist of a *caseous centre* (Fig. 470, *a*) and a *fibrocellular periphery* (*b*) which usually contains giant-cells. Under certain conditions the caseation may involve the entire tubercle. If the caseation does not affect the periphery, the fibrocellular tissue of the peripheral zone, sooner or later, becomes transformed into a pure *fibrous tissue,* so that a **fibrocaseous tubercle** (Fig. 471, *a*, *b*) is formed, the connective tissue of which is coarsely fibrillar or hyaline and poor in cells (*b*), and in the course of time usually becomes sharply defined from the caseous centre (*a*), so that the latter appears to be encapsulated by connective tissue. If the tuberculosis runs a favorable course the ca-

tre instead of caseating may undergo a connective-tissue metamorphosis (Fig. 472, *b*, *c*, *d*), so that the tubercle becomes changed into a **fibrous nodule.**

The *infectious nature* of the disease known as *tuberculosis* had already been determined by the experimental transmission of tuberculosis to animals (*Villemin*, *Lebert*, *Wyss*, *Cohnheim*, *Klebs*, *Langhans*, and others), before the discovery of the tubercle-bacillus. Nevertheless, it was a long time before the view that tuberculosis was an infectious disease received general acceptance, and opposition to this view has even to-day not wholly disappeared (*Middendorp*).

The peculiar behavior of the tubercle-bacillus toward stains—that is, its property of retaining the stain after treatment of the preparation with acids and alcohol, the so-called *acid-* and *alcohol-resistance*—makes it possible to demonstrate with relative ease the presence of tubercle-bacilli in the sputum or in the tissues, and to differentiate it from other bacteria. It should be noted, however, that other bacteria show these properties; the *bacillus of leprosy*, the *smegma-bacillus* (a bacillus very frequently found on the corona glandis, between the scrotum and thigh and in the folds between the labia majora and minora), further two different *bacilli found in butter* (one described by *L. Rabinowitsch* and *Petri*, the other by *Korn*), and finally also different bacilli cultivated by *Moeller* from *grasses* (timothy-grass) and from *cow-dung*. All these acid-resisting bacilli may under certain conditions lead to errors of diagnosis; for example, the smegma-bacillus in the examination of urine, the butter-bacilli in the examination of butter, the latter particularly, since the bacillus described by *Rabinowitsch*, when injected into the peritoneal cavity of guinea-pigs, causes a disease of the abdomen similar to true inoculation-tuberculosis, while the bacillus described by *Korn* causes a pseudotuberculosis in white mice (these animals showing but slight susceptibility to true tuberculosis). Acid-fast bacilli, which probably represent a variety of the Rabinowitsch butter bacillus, have been found in gangrenous foci in the lung (*Rabinowitsch*) as well as in the sputum of cases of pulmonary gangrene (*Folli*, *Mayer*, *Ophüls*, *Birt* and *Leishman*). *Moeller* has found acid-fast bacilli in nasal and pharyngeal mucus.

Since the tubercle-bacillus in cultures forms simple and branching threads (*Klein*, *Fischel*, *Coppen-Jones*, *Nocard*, *Maffucci*, and others) and bud- and club-like swellings, many authors are inclined to group it with the thread-fungi. *Lehmann* and *Neumann* designate it as *Mycobacterium tuberculosis*, *Coppen-Jones* as *Tuberculomyces*.

Since the tubercle-bacillus in caseous pulmonary foci (*Coppen-Jones*), and after direct injection into the parenchyma of the brain, kidneys, mammary glands, and testicles, as well as after the intra-arterial injection of large numbers of bacilli (*Babes*, *Levaditi*, *Schulze*, *Lubarsch*, *Friedrich*, and *Nösske*) forms, in addition to the ordinary colonies of bacilli, fungus-masses also resembling those of actinomyces, on the outer surface of which ray-like clubs radiate into the surrounding tissue, *Lubarsch* and others, in the assumption that the fungus-masses consist of branching threads, have classed the tubercle-bacillus with the actinomyces or ray-fungi. *Lubarsch* regards the ray-fungi as a sub-class of the *Streptothrices*, an intermediate group lying between the *Schizomycetes* and the *Hyphomycetes*, and characterized by the formation of clubs; and to this class he assigns also the butter- and dung-fungi mentioned above. According to *Friedrich* and *Nösske* the fungus-masses regarded as resembling those of actinomyces consist only of rods.

According to the investigations of *Hammerschlag*, *Ruppel*, *Sata*, and others, the tubercle-bacilli contain an abundance of fat, which under proper conditions may be demonstrated by staining with sudan (Sata). According to *Hammerschlag* the tubercle-bacilli contain twenty-seven per cent of substances soluble in alcohol and ether (fats, lecithin, poisonous substances), while other bacteria contain only 1.7–10 per cent of the same. The remaining substance insoluble in alcohol contains albumin and cellulose. Apparently the acid resistance of the bacilli is dependent upon the rich fat content, young bacilli which lack the fat covering are not acid-fast (*Marmorek*).

According to the investigations of *Prudden*, *Hodenpyl*, *Kostenitsch*, *Vissmann*, *Masur*, *Kockel*, and others, dead tubercle-bacilli, when introduced into the tissues of an animal by inoculation, or injection into the blood-stream, or through introduction into the respiratory passages, excite, at the point of deposit, inflammation and tissue-proliferation similar to that caused by living bacilli, and in the case of a large inoculation may lead also to suppuration. These changes differ, however, from those produced by living bacilli, in that the bacilli are destroyed after a few weeks and the nodules of granulation tissue heal through a transformation into fibrous tissue; and further, by the fact that the severity of the local tissue-proliferation is dependent wholly upon the amount of dead bacilli introduced, and that there is no spread of the process throughout the body. The dead bacilli must therefore contain substances (proteins) which cause inflammation and later also tissue-proliferation.

In addition to the local effects, the substance contained in the cell-bodies of the bacilli may also cause emaciation of the animal.

The *active substance of the bodies of the bacilli—tuberculin*—was first produced by *Koch* (1890) from six- to eight-weeks-old cultures in a weak alkaline veal-infusion, to which one per cent of peptone and four to five per cent of glycerin were added, by evaporation upon a water-bath to one-tenth of the original volume and filtering through a filter of earthenware and silicious marl. Later (1897) he dried highly virulent cultures of tubercle-bacilli in a vacuum-exsiccator, then triturated the dry substance, mixed it with distilled water and centrifugated it. The active principle is contained in the muddy precipitate thus obtained, which is again dried and triturated and dissolved in water to which twenty per cent of glycerin is added for the purpose of preservation. This tuberculin (designated by Koch as T. R.) is said to contain 10 mgm. of solid substance in 1 c.c. (prepared by *Meister, Lucius*, and *Brünning*).

Whether the tubercle-bacilli produce a true *toxin* is a question that has not yet been decided, but this is probably not the case; and in favor of this is the fact that localized tuberculosis clinically shows no symptoms of intoxication. The *tuberculins* obtained by various methods contain a *mixture of different substances* which, like the substances derived from other bacteria, excite inflammation. Perhaps they contain also specific albumin bodies which, in the organism, cause the production of specific *bactericidal protective forces*, either through the formation of *bacteriolysins* or of *agglutinins* and *precipitins* that act upon the bacteria. (See § 33.)

Through the investigations of *Arloing* and *Courmont* we know that an emulsion of *cultures of tubercle-bacilli* grown upon potatoes is agglutinated by the serum of tuberculous men and animals. Through an especial method *Koch* has prepared a fluid containing bacilli in which a clouding and a flocculent precipitate is produced by an agglutinating serum. The serum of healthy animals (rabbits, dogs, cow, and donkey) shows no agglutinating action when the test fluid is added to the serum in the proportion of 1:25; yet there are exceptions to this and horse serum usually shows an agglutinative power. According to *Koch* and *Romberg* the serum of children possesses no agglutinative power. After the fourteenth year it is very frequently present, probably as the result of latent tuberculosis. Through the treatment of an animal with dead or living cultures of tubercle-bacilli it is possible to produce a serum capable of agglutination (*Koch*) or to increase that already present, particularly easily in goats and donkeys.

Animals possessing the *power of agglutination* show a more or less high degree of *immunity against an artificial infection with tubercle-bacilli*, and the agglutinative power may therefore be regarded as an indication of the existence of protective substances.

In men suffering from tuberculosis the power to agglutinate is not usually shown in dilutions of 1:25. In advanced tuberculosis the agglutination power is usually wanting, since in the course of a malignant tuberculosis the protective substances are either not formed at all or at least only in small amounts. A mixture of pulverized tubercle-bacilli in 100 parts of water plus 100 parts of glycerin when injected in increasing doses (0.8 per cent salt solution, the first dose contains 0.0025 mg. of the cell substance of the bacilli) has, in the hands of *Koch*, increased the agglutination power of numerous consumptives (from 1 : 25 to 1:100 and 1:300), so that it may be assumed *that it is also possible to produce in consumptives a certain amount of protective substance.*

As to the *value of the old and new tuberculin of Koch* various writers differ. Its worth as a *diagnostic aid* is not questioned, particularly that of the old tuberculin, since small doses excite fever in tuberculous animals but not in healthy ones, yet there are exceptions also to this. The old tuberculin finds a use in the recognition and removal of tuberculous domestic animals. As a curative method (it is used in small doses in tuberculosis) it is praised by some, but at present its use is not very extensive.

During the last year much clinical interest has been excited over the diagnostic use of tuberculin in the *cutaneous reaction* ("*Pirquet's reaction*") and the *conjunctival reaction* ("*Calmette's reaction*").

Von Behring has succeeded in rendering cattle immune against virulent bovine tubercle-bacilli. He uses first cultures of human tubercle-bacilli which are less virulent for cattle, and begins with an intravenous injection of 1 mgm. of a serum-culture of a definite strength of infection. In younger animals the immunization can be much more easily produced than in older ones. *Von Behring* regards it as possible to feed nurslings with a milk of cows made immune against tuberculosis and thus to convey to them antibodies which may servé to protect them from infection.

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See also § 171.

§ 171. **Tuberculosis** is at the beginning a **local disease**, which occurs most frequently in the lungs, intestinal tract, and skin; that is, in places accessible from without. *Cases of cryptogenic infection* are by no means rare; in these the first demonstrable disease-changes appear in tissues concealed in the deeper portions of the body-parenchyma—as, for example, in the lymph-glands, adrenals, bones, joints, brain, tubes—and it is to be assumed that under certain conditions the bacilli enter the body without causing lasting changes at the point of entrance, so that they develop first in some distant organ to which they are carried by the blood or lymph, and through multiplication give rise to tissue-degeneration, to emigration of white blood-cells, and to proliferation of tissue.

The **local disease** usually begins with the formation of **miliary tubercles**—that is, cellular nodules of the kind described above—which arise in the tissue either singly or (in case of multiple infection) in great numbers simultaneously, or one after another (secondary dissemination of the multiplying bacteria). The tissue in the neighborhood of the individual tubercles, as well as that between the tubercles, shows some

times a more, sometimes a less pronounced appearance of inflammatory exudation and proliferation (of an especially cellular type); and through these processes there are frequently formed **large granulation-areas** in the infected connective tissue.

In the case of a *surface colonization of the bacilli*, as is possible in the alveoli of the lung and in the smallest bronchioles, an **exudative catarrhal inflammation** may be the first sign of the infection, while **proliferative processes** in the connective-tissue stroma and in the pulmonary vessels appear only at a later period.

In the mucous membranes and in the skin (Fig. 472) large areas of the mucosa and submucosa, or cutis respectively, may through the

Fig. [illegible]

formation of such granulations undergo a nodular or a diffuse fungous thickening. In the serous membranes there may develop large, fungous nodules in whose neighborhood the serosa is thickened and covered with a fibrinous exudate. In the synovial membrane of the joints and bursæ there often arise soft, spongy proliferations, the so-called fungous granulations (Fig. [illegible]); in the periosteum and bone-marrow round, grayish-red, or gray granulation-areas of varying size appear. All these areas have one feature in common—namely, in their neighborhood are found inflammatory infiltrations and proliferations of tissue, which bear the character of a **granulation tissue** (Fig. [illegible]), including characteristic non-vascular, cellular nodules—**tubercles** (Figs. 47?, 47?)—which often contain giant cells. In grayish-red tissues such as blood the tubercles may often be recognized by the naked eye as gray, or, when undergoing caseation, as white or yellowish-white nodules.

The *area of tuberculous granulation tissue* when once formed becomes larger in its further course of development by an **appositional growth**.

whereby the same processes, as just described, consummate themselves at the periphery. There may arise in this way, either within an infected organ, or upon the surface of such, nodules of large size, **solitary tubercles** (Fig. 475, *c*) as, for example, in the pia, brain, and upon the dura mater, which not infrequently resemble true tumors. Further, the tissue transformed by the tuberculous process or the newly formed tissue respectively, may suffer various fates; and there may be distinguished three chief forms of termination, which may, however, be combined in various ways.

In a first group of cases the production of connective tissue forms the most striking feature, and there results a **connective-tissue** induration of the diseased tissue (Fig. 476) with the development of a dense, fibrous connective tissue (*a*). If the process does not come to a standstill, there may be found in association with the fibrous tissue new *proliferations* of *granulation tissue* (*b*), and often also a larger or smaller number of typical *tubercles* (*c*). If the process comes to a complete **standstill** and to a **cure of the infection**, the entire area may come to consist of a dense fibrous tissue (Fig. 477, *a*, *b*) which in part shows a nodular arrangement (*a*), and in part is more hyaline and homogeneous in character. In the lungs such connective-tissue nodules contain more or less carbon-pigment (Fig. 477).

FIG. 474.—Tuberculous granulation tissue from the synovial membrane of the knee-joint (Müller's fluid, Bismarck brown). *a*, Connective tissue; *b*, granulation tissue; *c*, tubercle. × 60.

A second form of termination is a **combination** of **caseation** and **fibrous induration** comprising dense fibrous tissue (Fig. 478, *b*, *d*) and caseous foci (*a*) of varying size.

The third termination consists essentially in **caseation**, the tubercu-

FIG. 475.—Large solitary tubercle of the pia mater of the cerebellum in vertical section. *a*, Cerebellum; *b*, dura mater adherent to the tubercle; *c*, laminated tubercle; *d*, gray peripheral zone adherent to the dura mater and beset with yellowish-white, nodular deposits. Natural size.

lous granulation tissue dying and producing no connective tissue at all, or only in such a slight amount that it is completely overshadowed by the caseous masses (Fig. 479, *c*).

Both the fibrocaseous and the purely caseous areas may become

FIG. 476.—Tuberculous induration of the lung (alcohol, hæmatoxylin, and eosin). *a*, Dense, fibrous tissue; *b*, cellular granulation tissue; *c*, giant-cells. × 40.

FIG. 477.—Tuberculous induration of the lung (alcohol, hæmatoxylin, eosin). *a*, Homogeneous fibrous nodules poor in cells and in part pigmented; *b*, diffuse induration of the lung. × 24.

healed, through their ***encapsulation from the surrounding tissues*** by connective tissue (Figs. 478, *b*; 479, *c*, *e*). Such a healing can be regarded as complete only when in the connective-tissue capsule (Fig. 479, *c*, *e*) and

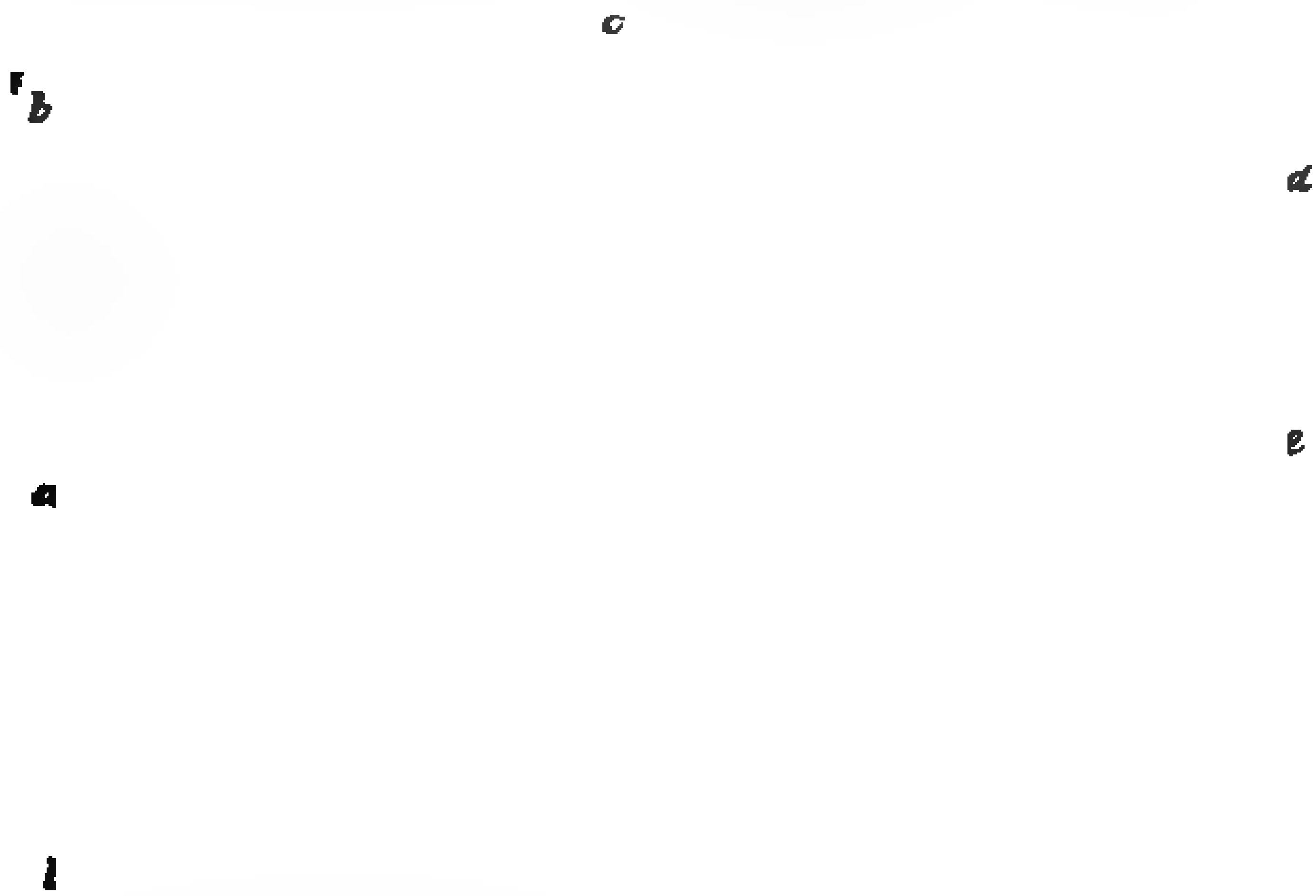

FIG. 478.—Encapsulated area of caseation of the lung with induration and eruption of tubercles in the neighborhood (formalin, alcohol, hæmatoxylin, eosin). *a*, Caseous area; *b*, fibrous capsule; *c*, tubercle; *d*, indurated lung tissue; *e*, area of granulation tissue. × 40.

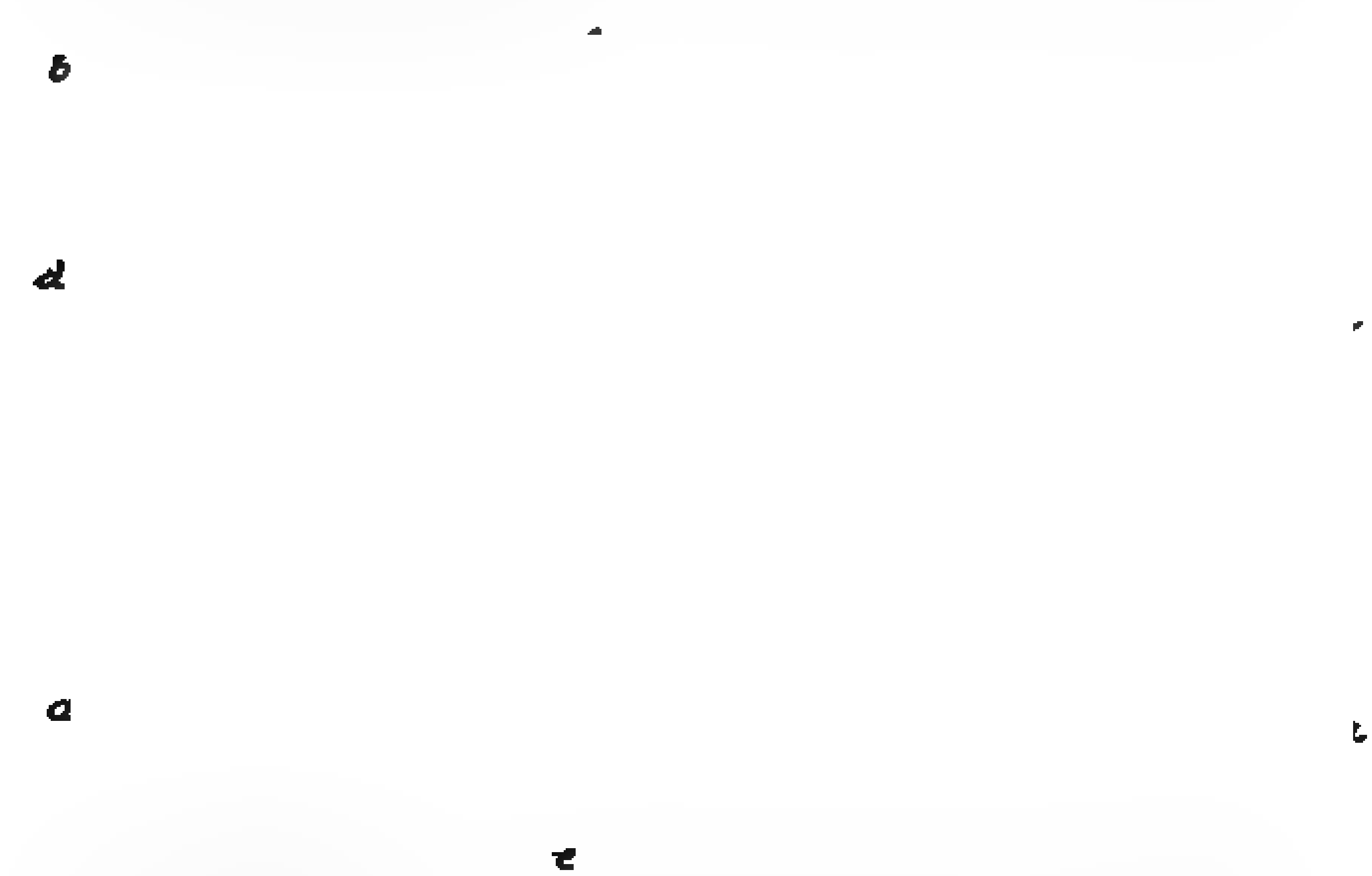

FIG. 479.—Encapsulated area of tuberculous caseation in the lung. *a*, Normal lung tissue; *b*, pleura; *c*, area of caseation; *d*, remains of elastic fibres in the area of caseation; *e*, small encapsulated caseous nodules; *f*, thickened pleura. × 15.

its neighborhood (*a*) neither fresh granulation-tissue **areas nor tubercles** are still present. Occasionally **calcification** of the encapsulated **caseous** mass may occur as a further sign of the termination of the process.

The **caseous masses** of tuberculous foci are sometimes **firm**, sometimes soft, and in the latter case very often suffer a **disintegration** and **liquefaction** leading to the formation of milk-white, crumbling, and pultaceous or even thin fluid masses, so that the tuberculous **area comes** to present the picture of an **abscess** surrounded by a wall (designated as *cold abscess*). Rupture and emptying of the same externally **leads** to the

FIG. 480. Tuberculous cavern in the tibia (alcohol, picric acid, hæmatoxylin, carmine). Transverse section. *a*, Periosteum; *b*, rarefied cortex; *c*, periosteal deposit of bone; *d*, fibrous tissue on the inner surface of the cortex; *e*, granulation tissue containing tubercles; *f*, sequestrum with bony trabeculæ infiltrated with granulation tissue; *g*, union of the granulation tissue with the sequestrum; *h*, cavity that had been filled with pus and caseous masses. × 3½.

formation of **cavities** or **caverns** and **fistulous passages** accessible from without, and, when there is a wide opening, to **ulcers**.

Disintegration and cavity-formation occur particularly in the lung, and may there lead to the formation of cavities as large as a man's fist or larger. They also occur not infrequently in caseating lymph-glands, and in caseous foci in the kidneys, brain, muscles, skin, and bones (Fig. 480). The cavities (*h*) contain in the beginning the liquefied tuberculous tissue, in which not infrequently remains of the original tissue may be recognized in the form of sequestra (*f*). After the evacuation of the contents the wall may furnish material sufficient to fill the cavity again either through the secretion of pus or through the breaking-off of necrotic tissue. *Hæmorrhages* not infrequently arise through the erosion of blood-vessels.

The walls of the caverns and abscesses are usually lined by caseating granulation tissue containing tubercles (Fig. 480, *e*); the surrounding tissue becomes indurated in part, and in part the seat of caseating foci.

Ulcers occur most frequently in the mucous membranes (Fig. 481, *h*) and in the skin, since the softening caseous masses in these regions most

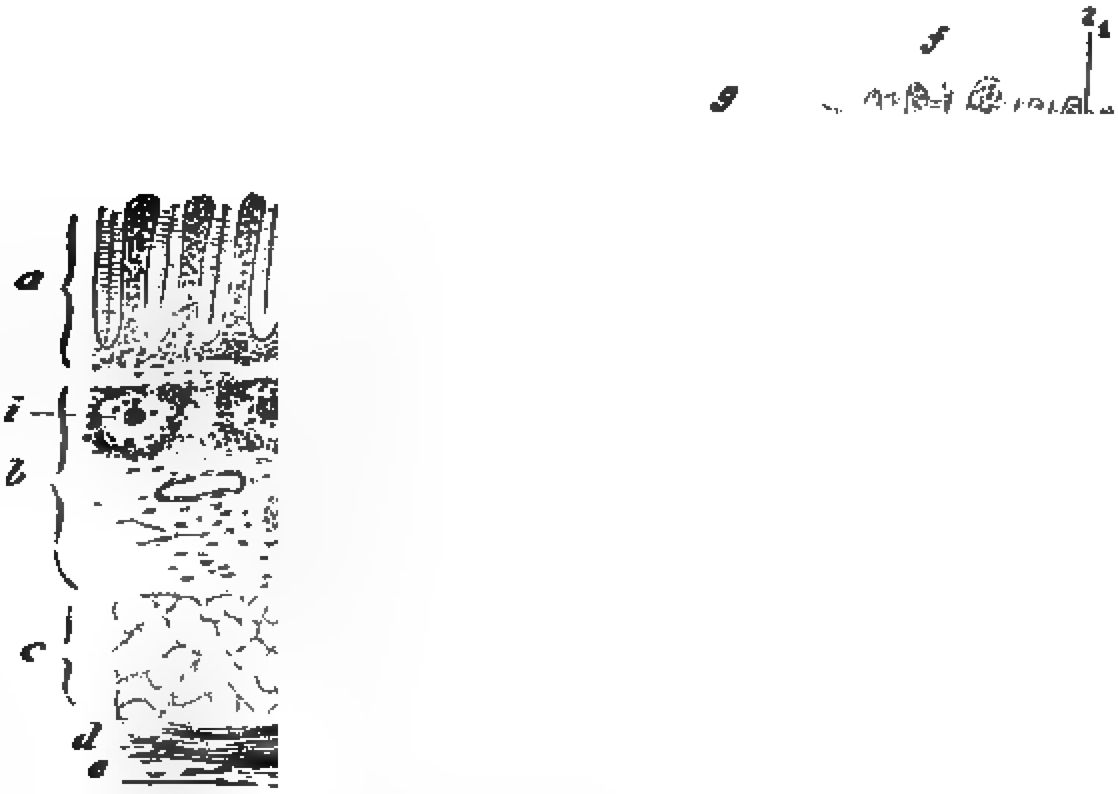

FIG. 481. Tuberculous ulcer of the intestine with eruption of tubercles in the neighborhood (alcohol, Bismarck brown). *a*, Mucosa; *b*, submucosa; *c*, muscularis interna; *d*, muscularis externa; *e*, serosa; *f*, solitary follicle; *g*, mucosa infiltrated with cells; *h*, ulcer; h_1, area of softening; *i*, recent, i_1, caseous tubercle. × 30.

frequently break through to the surface. The edges and base of the ulcers are surrounded by an inflammatory zone of infiltrated granulation tissue, often also containing tubercles.

FIG. 482. Beginning tuberculosis of the lung without catarrh (alcohol, orcein). *a*, Caseous area with remains of elastic tissue; *b*, normal lung tissue; *c*, pleura with tubercles; *d*, *e*, tubercles in the neighborhood of the caseous area; *f*, tubercle in the pleura; *g*, periarterial, *h*, peribronchial, *i*, perivenous tubercles of the lymph-vessels; *k*, new-formation of fibrous tissue beneath the limiting elastic layer of the pleura. × 16.

If a tuberculous focus does not become healed through tissue-inte[illegible] ration, sequestration or encapsulation of the dead tissue, or through t[illegible] removal or death of the bacilli, there exists the danger of metastasis.

This takes place first by the lymph-channels; and a part of the p[illegible]

FIG. 498.—Beginning tuberculosis of the lung in a two-year-old child. Horizontal section through [illegible] right lung (Müller's fluid, carmine). a, Caseous area in the region of the anterior border; b, [illegible] inner border free from tubercles; c, transverse section of the bronchus; d, d_1, caseating lymph-glan[illegible] pulmonary vein; f, point where the vein e has become adherent to the lymph-gland d_1; caseous degener[illegible] tion of the vein-wall has also begun at the same point; g, tubercles in the lymph-vessels of the pulm[illegible] parenchyma; h, periarterial, i, peribronchial, k, perivenous, l, pleural tubercles; m, tubercle of [illegible] vessel at hilum of the lung. × 2½.

ure of a progressive tuberculosis is the development of tubercles in the lymph-spaces and in the walls of the lymph-vessels (Figs. 481, i, i_1; 482, e, f, g, h, i; 483, g, h, i, k, l, m) in the neighborhood of the primary focus. The **lymphogenous miliary tuberculosis** is in some cases limited to the immediate neighborhood of the primary focus (Fig. 482), at other times it involves larger areas and may, for example, extend from a caseating tubercle in the lung (Fig. 483, a) over a large part of the pulmonary lymphatic system (g, h, i, k, l, m). These lymphangoitic tubercles present the appearance of bright gray nodules, often surrounded by a red zone, and consist essentially of the same structure as the primary focus.

FIG. 484.—Eruption of tubercles in a lymph-gland (alcohol, hæmatoxylin). a, Tubercle; a_1, caseous tubercle; b, tissue of the lymph-gland; c, giant-cell in the centre of a tubercle; c_1, giant-cell at the edge of a caseous focus; d, large-celled tissue between the tubercles; e, blood-vessel. × 150.

The *lymph-glands* may be affected very early (Fig. 483, d, d_1), whereupon tubercles develop in them (Fig. 484, a, a_1), leading through successive crops of the same to a more or less marked enlargement and finally to a caseation of the glands (Fig. 483, d, d_1), or to an induration, or to a combination of these processes. The *thoracic duct* may become infected from caseating and disintegrating lymph-glands, and through this channel an infection of the blood may also take place.

Very often the **formation of metastases takes place also through the blood-stream**; in the first place by the entrance of bacilli through the lymph from the thoracic duct as mentioned above, but very often also as the result of the *direct entrance of bacilli into the circulating blood.* In tuberculous tissue the bacilli may pass directly into small veins, though the obstruction to the circulation due to the closure of the vessels usually prevents their further dissemination. Often enough the bacilli gain entrance into the larger veins—as, for example, through the adhesion of caseating lymph-glands at the hilum of the lungs (Fig. 483, d_1) with the neighboring veins (e, f), the tuberculous process involving the vein-walls by direct extension. Moreover, an *infection of numerous veins* with tubercle-bacilli may occur in the neighborhood of a tuberculous focus, so that the small veins of an entire vascular system may present a well-marked tuberculous disease—that is, an inflammatory granulation-proliferation of the vessel-walls with the formation of tubercles and subsequent caseation (Fig. 485, b), so that, if thrombosis does not occur, large numbers of bacilli may enter the blood-stream from the diseased walls. In rare cases the arteries, particularly the pulmonary arteries, may become tuberculous through infection from the surrounding tissues, and so may give off bacilli to the blood-stream.

The transportation of the bacilli through the blood-stream gives rise to a **hæmatogenous miliary tuberculosis**—that is, to an eruption of miliary tubercles (Fig. 486, *a*) at those places where the bacilli become lodged and multiply. Just where these places will be, and how numerous the tubercles, depend upon the location of the point of rupture and the number of bacilli entering the blood. The entrance of many bacilli into the blood may lead to a *general hæmatogenous miliary tuberculosis.*

If the bacilli have entered the blood-stream in small numbers and have been deposited in only one organ, and if death does not ensue, there arises in this organ a progressive *hæmatogenous local tuberculosis,* which runs a course similar to that of the primary focus coming from without.

Fig. 485.—Tuberculosis of the veins in the neighborhood of a tuberculous retroperitoneal lymph-gland (formalin, hæmatoxylin, eosin). *a*, Tuberculous lymph-gland with giant-cells and caseous foci; large blood-vessels at the periphery; *b*, veins whose walls are thickened by tuberculous granulation tissue, the inner layers of which show caseation; *c*, fat tissue. × 28.

The **exudative inflammation accompanying the lymphogenous and hæmatogenous eruption of tubercles** is sometimes more, sometimes less pronounced, and is usually most severe in the meninges and in the lungs.

Should a tuberculous focus in the lung break into the bronchi, as the result of the softening of a caseous area, or if a caseating focus in the kidney should invade the kidney-pelvis, there will result a **dissemination of tubercle-bacilli over the surface of the mucous membranes.** From the bronchi the bacilli spread into the trachea, larynx, mouth-cavity and thence into the alimentary canal; through aspiration during deep quick inspiration, they may be carried into other portions of the lungs as yet unaffected. From the kidneys the bacilli may be spread throughout the descending urinary passages.

A **secondary infection** may also result from this spreading of the bacilli, yet only a small percentage of the bacilli thus distributed give rise to an infection; and experience has taught us that only certain portions of the mucous membranes are susceptible to infection—particularly

the tonsils and the lymphadenoid tissue of the small and large intestines, while the œsophagus and stomach are almost immune; and in the case of the descending urinary passages, the kidney-pelvis, the ureters, and bladder are usually infected while the urethra almost always remains uninvolved.

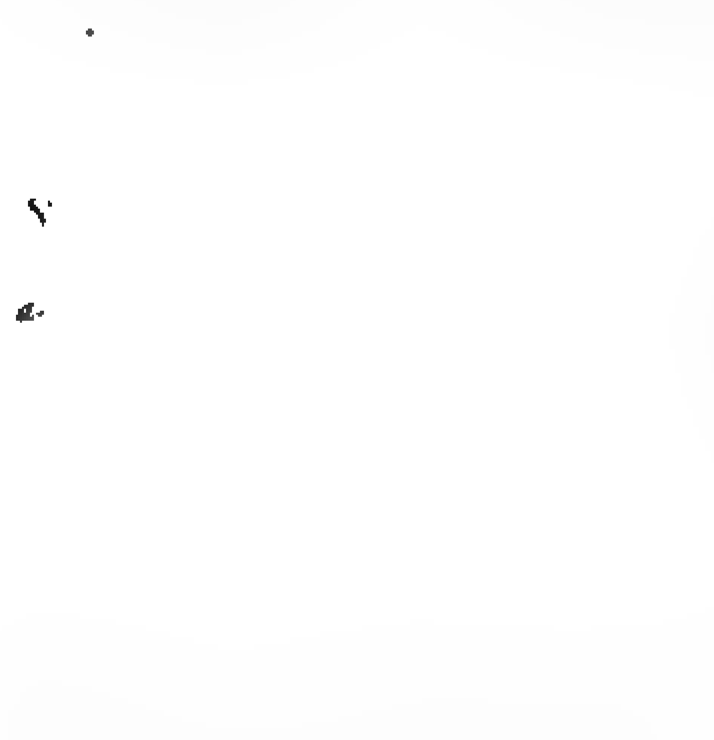

FIG. 486.—Hæmatogenous miliary tuberculosis of the liver (alcohol, carmine). *a*, Developed tubercle in the connective tissue about the portal vein; *b*, collection of leucocytes. × 150.

If **bacilli enter the great body-cavities** they can also spread over the surfaces of the serous membranes, infect the latter, and excite a diffuse inflammation and formation of nodules (Fig. 487). A new-formation of connective tissue may follow later.

Should tubercle-bacilli be present in the circulating blood of a woman during pregnancy, the **infection of the placenta and fœtus** may follow, so that the child will be born already infected. In so far as data concerning this point exist, this event is not of frequent occurrence; and it is more usual for *children of tuberculous parents to become infected after birth.* A conceptional infection of the embryo through infected semen has not yet been demonstrated, and is very unlikely.

Secondary infections are not infrequently associated with that caused by tubercle-bacilli, and this occurs particularly when the disintegration-cavities or ulcers are accessible from without. *Secondary infections of tuberculous lungs* are of very frequent occurrence, and are due particularly to *streptococci* and *staphylococci, pneumococci, influenza-bacilli, micrococcus tetragenus,* and *bacterium coli.* Many authors are inclined to refer all severe inflammatory exudations accompanying pulmonary tuberculosis to such secondary infections; but this is not correct in so far that the formation of tubercles by tubercle-bacilli may be accompanied by inflammatory exudations of such severity that

FIG. 487.—Tuberculosis omenti (Müller's fluid, carmine). *a*, Centre of tubercle; *b*, cells of epithelioid character; *c*, lymphatic elements; *d*, proliferating epithelium (endothelium) in the neighborhood. × 200.

serous or serofibrinous, or pure fibrinous, or fibrinopurulent exudates may collect in large quantities in the tissues (in the pulmonary alveoli, on the pleura, and in the subarachnoideal space, etc.). A high (septic) fever, rapid destruction of tissues with a tendency to suppuration, and an unusually severe inflammation, in part of a hæmorrhagic character, point to a secondary infection. Nevertheless, it is often impossible to determine, without a special investigation directed to this point, whether a pure tuberculosis or a mixed infection is present.

For the treatment of tuberculosis with bacterial extracts and curative serum see § 32.

The question as to how often **tuberculosis is transmitted by the passage of bacilli from the mother to the child** is still an open one. It has, however, been shown by *Schmorl*, *Birch-Hirschfeld*, and *Landouzy* that in cases of miliary tuberculosis in pregnant women, tubercle-bacilli are present both in the intervillous spaces and in the blood of the chorionic vessels, and that the liver of the fœtus may contain bacilli. Further, cases of tuberculosis of the placenta also occur (*Schmorl*, *Kockel*, *Lungwitz*, *Warthin* and *Cowie*), which may be regarded as stages on the way of the tubercle-bacillus from the mother to the fœtus.

Cases of tuberculosis occurring at an early period of life, reported by *Demme*, *Baumgarten*, *Rilliet*, *Charrin*, and others, as well as the statements of *Armanni*, *Landouzy*, and *Martin*, that the inoculation of portions of the organs of human fœtuses obtained from tuberculous mothers produced tuberculosis in guinea-pigs, speak in favor of a passage of tubercle-bacilli from the mother to the fœtus. Still more important are the experimental investigations of *de Renzi* and *Gärtner*, who succeeded through the inoculation of pregnant guinea-pigs, white mice, and rabbits in producing tuberculosis in a part of the young born of these animals. *Gärtner* is consequently of the opinion that under certain conditions tubercle-bacilli may pass from the mother to the fœtus in the case of both animals and man. Finally, *Maffucci* and *Baumgarten* succeeded in effecting a transfer of tubercle-bacilli to impregnated hen's eggs, and discovered that the infection did not disturb the development of the chick, but, on the contrary, the bacilli that were taken up by the embryo remained in the tissue of the latter without multiplying to any extent, later to cause a tuberculosis in the body of the hatched-out chick. According to the evidence of anatomical investigations *a placental transmission of tuberculosis to the child cannot be doubted.* On the other hand, a conceptional transmission of tuberculosis from the father to the embryo has not yet been proved. Moreover, according to the investigations made up to the present time it may be emphasized that *tuberculosis is to be referred usually to an extrauterine infection* and that *children of tuberculous parents* suffer from tuberculosis so frequently because they are *more exposed to an infection with tuberculosis* than are the children of healthy parents. An especial *predisposition to tuberculosis in the children of tuberculous parents* has not yet been demonstrated.

In animals a transmission of tuberculosis to the fœtus seems occasionally to occur, according to the reports of *Zippelius*, *Jessen*, *Pütz*, *Grothans*, *Malvoz*, *Lydtin*, *Brouvier*, *Adams*, and others. *Johne* was not only able to demonstrate in a fœtal calf the presence of miliary nodes and larger nodules in the lungs, liver, and various lymph-glands, but also to show the presence of characteristic bacilli in the lesions.

From the side of clinicians and physicians the so-called **scrofula** has been many times regarded as an especial pathological condition of the organism of the child, predisposing it in an especial degree to tuberculosis. As scrofulous are regarded those children who permanently or at least very frequently suffer from inflammations of the mucous membranes (nose and its accessory cavities, conjunctiva, middle ear), as well as of the skin, also from swelling of the lymph-glands leading occasionally to necrosis and suppuration, finally also from chronic inflammations of the bones and joints, and who present a flabby, pale, often bloated appearance. In many cases these symptoms are due to tuberculosis; in other cases they are caused by an infection with streptococci or staphylococci, or are the results of syphilis. Scrofula is not a disease-entity, but is only an especial symptom-complex belonging to different diseases. Whether the affected children possess an *especial predisposition to all these infections* which may be designated as *scrofula* is difficult of proof. The organism of the child is in general easily infected by these agents, and the frequent illness of certain children due to these infections may be referred to a lack of cleanliness, or to especial conditions of the environment of the child, or to frequent injuries, etc., as well as to an especial predisposition of the child itself.

Von Behring has in recent years upheld the view that tuberculosis is almost always the result of bacilli entering through the intestine in infancy, and that later infections play a wholly subordinate rôle. This theory is correct in so far as the long-known fact is concerned, that the intestine of infants takes up the bacilli more easily than the adult intestine, and that the infection is not always manifest at the point through which the bacillus enters, but develops first in those organs, the lymph-nodes, lungs, brain, bones, etc., to which it has been carried by the blood or lymph. Infection with tubercle-bacilli may occur at any age. Further, the primary intestinal infection is not the dominating one, but the infection of the respiratory tract is. The latter results usually from the direct entrance of the bacilli into the respiratory parenchyma. Primary infection of the nose, larynx, trachea, and bronchi also occurs, but is relatively much less frequent than the primary lung-affection.

Calmette's view of the intestinal organ of anthracosis has also been turned as an argument favoring the ingestion-theory of tuberculosis. Much has been written upon this subject during the last several years, and while the opinion of the majority of pathologists favors the aërogenous nature of tuberculous infection in late childhood and in adult life, the etiological importance of infection through the intestine in infancy has been increased to such an extent that this mode of infection cannot be disregarded practically.

Tuberculosis of mammals is observed most frequently in the case of *cattle*, and presents in general a course similar to that of the disease in man, though the granulation-areas develop more frequently into larger tumor-like nodules, particularly so in cattle, and the tendency to a generalization of the disease is less. The tuberculosis of the serous membranes which is often designated as **pearl disease** (*"Perlsucht"*) begins with the formation of small nodules, leading then to a more marked proliferation of the connective tissue, giving rise to the formation in the thickened serosa of nodules of the size of a pea or bean or even as large as a hen's egg or man's fist (Fig. 488), which in the beginning are soft and sarcoma-like, but later become firmer and denser and often enclose calcified areas of caseation. The form of the proliferation is sometimes villous-like and warty, at other times of a mulberry- or grape-like form, cauliflower-like or even polypoid.

FIG. 488.—Growths from the pleura in a case of bovine tuberculosis ("Perlsucht").

Next to cattle the *hog* is most frequently affected with tuberculosis, more rarely the horse, goat, sheep and cat, and still more rarely the dog.

Of *wild animals* in captivity, the ape, lion, tiger, bear, jackal, panther, jaguar, giraffe, and dromedary easily acquire tuberculosis. Of the small animals used for experiment the guinea-pig is the most susceptible. After subcutaneous inoculations there results a progressive tuberculosis which kills the animal in from about four to eleven weeks. In rabbits an inoculation tuberculosis may heal. Field mice and white mice are infected with difficulty.

Tuberculosis is of frequent occurrence in **birds** (chickens, pigeons, pheasants, and parrots), and is usually localized in the abdominal organs.

The cultures of tubercle-bacilli from man are dry, warty, or scaly and lustreless; those of avian tuberculosis moist, wrinkled, and soft, and moreover grow best at 43° C. Dogs are wholly immune to avian tuberculosis, but not to human tuberculosis. The intraperitoneal inoculation of mammalian tuberculosis (*Leray*) causes in rabbits numerous caseous foci in the liver and spleen with few giant-cells and scanty bacilli, and in the lungs numerous caseous nodules containing numerous bacilli. Inoculations into these animals of chicken-tuberculosis, on the other hand, cause a scanty production of non-caseating cellular proliferations containing giant-cells and great numbers of bacilli.

According to *Maffucci*, *Martin*, *Gärtner*, and others, the inoculation of human tuberculosis into chickens does not produce tuberculosis, but the bacilli remain alive

for weeks [illegible] the body of the chicken. Pigeons [illegible] die after intraperitoneal inoculation [illegible] tubercles are found in the tissues; the liver and lungs may contain living bacilli [illegible] days after the inoculation. In guinea-pigs (*Straus*) the bacilli of human tuberculosis cause much more severe changes than do the bacilli of chicken-tuberculosis. In mice infected with avian tuberculosis (*Weber* and *Bofinger*) there occurs a moderate increase of the bacilli without [illegible] and without any marked reaction on the part of the tissue. When kept in the mammalian body (guinea-pigs) and mice [illegible] the virulence of avian bacilli for guinea-pigs is not changed. Whether man is susceptible to avian tuberculosis is still an open question.

The **question whether the tuberculosis of animals, particularly of the domestic animals, is identical with that of man** has been the subject of lively discussion during recent years. The majority of writers believe in their identity. *Koch* and *von Schweinitz* [illegible]. In favor of the latter view may be taken the fact that the bacilli of different sources show differences in cultures, cultures of avian tuberculosis in particular showing essential differences from those of human tuberculosis; further, inoculations of human tubercle-bacilli into domestic animals, for example, into cattle, are either negative or cause a milder disease than that resulting from the inoculation of bacilli obtained from sick cattle. In spite of these facts it cannot be doubted that we have to deal not with different forms of disease, but that the tuberculosis of man and that of the domestic animals are identical diseases produced by **varieties of the same species of bacillus.** When the bacilli increase for a long time within the same species of animal they acquire properties that make them [illegible] other species and they are with difficulty made to grow in the latter. Human tuberculosis is nevertheless still directly transmissible into many animals, and man may be infected with the bacilli of mammalian tuberculosis. [illegible] milk and meat containing tubercle-bacilli can [illegible] tuberculosis [illegible] man, and the attendants of cattle can be infected from sick animals also through [illegible] of the respiratory tract. The avian strain of tubercle-bacilli is the farthest removed in its properties from the human strain. In [illegible] tuberculosis the bacilli of which are identical in their properties with those of the bacilli of human tuberculosis.

Tuberculosis occurs also in cold-blooded animals (fish, [illegible]), [illegible] is likewise caused by an acid-fast bacillus that possesses an optimum of growth at [illegible] and grows at temperatures of [illegible]. It has been assumed (*[illegible]* and others) that this bacillus is also a variety of the bacillus of mammalian tuberculosis. [illegible] has attempted to [illegible] guinea-pigs against tuberculosis by inoculating them with the [illegible] of the tuberculosis of cold-blooded animals.

As **pseudotuberculosis** may be classed all those affections characterized by the formation of cellular and fibrous nodules [illegible] in part also undergoing necrosis [illegible] which are similar to tubercles, but which are not caused by [illegible] bacillus. According to the [illegible] the following forms may be distinguished:

[illegible]

hog, goat, cat, hare, roe, stag, and chamois, and it is caused by different forms of *Strongylus* and by *Pseudalius capillaris* (*Müller*); it is therefore a vermian pseudotuberculosis.

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See also § 170.

(Tuberculosis of Animals. Pseudotuberculosis.)

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§ 172. **Syphilis** is, like tuberculosis, an infectious disease, which, proceeding from a local infection, spreads throughout the organism by means of the blood- and lymph-channels, and leads to the formation of localized inflammations and proliferations of granulation tissue, which, however, do not present so characteristic a structure as does the tubercle.

In 1905 *Schaudinn* and *Hoffman* announced the constant occurrence in syphilitic lesions of a characteristic organism. Control examinations of non-syphilitic lesions failed to reveal it. To the newly discovered parasite the name of **Spirochæte pallida** was given. Corroboration of the finding of *Schaudinn* and *Hoffman* was soon forthcoming from a large number of investigators in all parts of the world. It was found to be constantly present in the primary lesions, in all forms of secondary and tertiary lesions, in the blood, lymph, and cerebrospinal fluid of syphilitics, in the lesions of congenital syphilis and in the blood, lymph, cerebrospinal fluid and organs of cases of congenital syphilis, and in the placenta of such cases. It has also been demonstrated in the experimental syphilis of apes (*Metschnikoff*). But little evidence has been brought against its position as the etiological agent of syphilis, and the majority of writers now accept it as such. Control investigations have been particularly unanimous as to its absence in non-syphilitic lesions. Although the organism has not been cultivated and the third and fourth laws of Koch have not yet been fulfilled, we are justified from the evidence now at hand in considering the *presence of the Spirochæte pallida as diagnostic of syphilis, even if we cannot show positively that it is the causal agent.*

The *Spirochæte pallida* is a delicate, non-refractile spiral organism, varying in length from 2–20 μ, the average length being about 4–14 μ. The spirals are tight and corkscrewlike, fading out at the pointed ends. They vary in number from three to twenty-five or more. The large number of spirals in proportion to the length of the entire organism is very characteristic. The whole organism is usually somewhat curved. Delicate terminal flagella have been observed. The spiral form is retained when the organism is at rest. It has the power of rotation on its long axis, of moving forward and backward, and of making whip-like undulations. A nucleus has not been positively demonstrated. It does not bear spores and no evidence of transverse division has been observed. *Schaudinn* believed that it possesses an undulating membrane. At the present time it is not definitely decided whether to regard the organism as a protozoon or as a spirillum. *Schaudinn* favored the former view. In accordance with this belief the names *Spironema* and *Treponema pallidum* have been proposed for it.

The *Spirochæte pallida* stains very poorly, but can be easily demonstrated in smears from primary lesions by staining with Wright's stain, the Romanowsky or the Giemsa stain. It is very important that the smears be stained as soon as made; it often cannot be found in smears that are not perfectly fresh. From the *Spirochæte refringens* it is distinguished by its delicacy, pale staining, and the number of its spirals and their tight, corkscrew arrangement. The refringens is larger, thicker, more refractile, stains easily, and has broad, loose wavy spirals, and its ends are usually blunt. Levaditi's method may be used for staining the pallida in sections. For literature concerning *Sp. pallida* see *Folia Hæmatologica,* 1905, 1906, 1907.

The poison through whose inoculation syphilis is produced occurs only within the human organism, where it is alone reproduced, and is communicated to other individuals only by direct or indirect transfer. Metschnikoff, Roux, Lassar, and Neisser have succeeded in conveying syphilis to anthrapoid apes (the chimpanzee) through the inoculation of syphilitic tissue. When implanted in an organism the infective agent

excites inflammatory processes of the most varied intensity and extent—from a simple local transitory hyperæmia to the production of large exudates or tumor-like granulations, or extensive hyperplasias of connec-

FIG. 489. Initial sclerosis (alcohol, hæmatoxylin, eosin). *a*, Corium, slightly inflamed; *b*, initial sclerosis; connective tissue infiltrated with cells; *c*, rupture of the cells into the epithelium; *d*, *e*, lymph-vessels filled with round cells. × 25.

tive tissue.. The child of a mother infected with syphilis may receive the infection through the placenta.

If the first focus of inflammation develops at the point of infection, which is usually located in the skin or mucous membranes (mouth, throat, mucosa of genital apparatus), there is formed first a papule which spreads toward the surface, and within eight to ten days after its appearance forms scales, or ulcerates and secretes a small amount of serous or purulent fluid which dries to a scab; at the same time its base becomes hardened and forms a thick disc-like or a thin parchment-like deposit in the skin. Occasionally a vesicle is also formed, and this becomes an erosion, and then an ulcer with scanty secretion and having an indurated base. In still other cases an ulcer is first formed, and the base becomes indurated subsequently.

FIG. 490.—Section from a syphilitic initial sclerosis (alcohol, alum carmine). *a*, Round-cell infiltration; *b*, large mononuclear formative cells; *c*, multinuclear giant cells. × 250.

The induration is called the **initial sclerosis** or the ***Hunterian induration*** (Fig. 489, *b*); the **ulcer** is known as a ***hard chancre***. The former is caused essentially by a collection of small ***round cells*** (Figs. 489, *b*; 490, *a*) in the spaces of the connective tissue. Occasionally ***epithelioid cells*** (Fig. 490, *b*) and *isolated giant-cells* are also formed ...

With these changes the height of the process is reached; the greater part of the tissue disintegrates and ulcerates, or is absorbed after disintegration. A part of the cells are utilized in the formation of scar tissue.

Within the area of the initial sclerosis and its immediate neighborhood the lymph-vessels (Fig. 489, *d*, *e*) are dilated and filled with leucocytes. Later, after the lapse of a certain length of time the lymph-glands, the skin, and the mucous membranes become involved in inflammatory processes (symptoms of the secondary stage). Still later, there follow syphilitic inflammations of the internal organs and the bones (tertiary stage). These are in part like other non-syphilitic inflammations, but special forms of granulation tissue are sometimes produced. The syphilitic affections of the skin which are grouped under the term **syphilides** form sometimes only red spots, sometimes larger or smaller papillary elevations which may be associated with the formation of vesicles and pustules as well as with the production of scales. Accordingly,

FIG. 491.—Condyloma latum ani (alcohol, Bismarck-brown). *a*, Horny layer; *b*, mucous layer of the epidermis; *c*, corium; *d*, loosened horny layer infiltrated with small cells; *e*, swollen, *f*, swollen and infiltrated mucous layer; *g*, epithelial cells containing round cells; *h*, granular masses of coagula; *i*, swollen papillary body infiltrated with cells and fluid; *k*, corium, swollen, and infiltrated with cells, fluid and coagulated albumin; *l*, dilated lymph-vessels filled with clots; *m*, sweat-glands. × 150.

the different forms of cutaneous syphilides have been called by different names, as follows: *Roseola syphilitica*, and *papular*, *vesicular*, *pustular*, and *ulcerative syphilides* as well as a *psoriasis syphilitica*. A common element in all these affections is a more or less marked inflammation, which is characterized particularly by a tissue-infiltration and in part also by proliferation. Thus, for example, in the *large papular syphilide* or *condyloma latum* there is a beet-like elevation of the skin caused by an infiltration of the papillary body (Fig. 491, *i*), the corium (*k*), and

FIG. 492.—Meningo-encephalitis syphilitica gummosa (Müller's fluid, alcohol, hæmatoxylin). *a*, Brain cortex; *b*, inner meninges; *c*, vein surrounded by cellular exudate; *d*, fresh cellular granulation tissue; d_1, fibrocellular granulation tissue; d_2, caseated granulation tissue; *e*, artery with markedly thickened intima and adventitia infiltrated with cells; *f*, cellular infiltration of the pia-sheaths of the cortical vessels; f_1, perivascular cellular infiltration of the cortical substance; *g*, diffusely spreading cellular infiltration invading the brain-substance. × 14.

FIG. 493.—Syphilis of the skull-cap. *a*, Periosteum; *b*, bony trabeculæ; *c*, small-celled infiltration of the marrow; *d*, necrotic infiltrated marrow-tissue; *e*, periosteum proliferating into the bone; *f*, fibrous endosteum; *g*, osteoclasts and Howship's lacunæ. × 40.

also the epithelium (*e*, *f*, *g*, *h*) with cells and a fluid exudate which coagulates, causing hardening of the tissue. If the horny layer of the epidermis becomes macerated, these masses of exudate may appear upon the surface, and give rise to a moist condition of the condyloma. In the pustular syphilides the inflammation leads to a purulent liquefaction of the epithelium, and in the ulcerating forms also of the papillary body and of the corium, so that *ulcers* result.

Inflammatory changes similar to those in the skin appear in the secondary stage of syphilis, also in the mucous membranes, particularly of the mouth, throat, and respiratory passages.

The syphilitic lesions of the tertiary stage, appearing in the internal organs, in the glands, bones, muscles, subcutaneous and submucosal tissues, in the meninges of the brain, etc., in so far as they consist not only of slight degenerative and inflammatory processes or hyperplasias of connective tissue without characteristic features, appear as formations which are usually designated as **gummata** or as **syphilomata** (Virchow). In its early stages the gumma, as well as the broad condyloma, represents an inflammatory process localized to one tissue-area; but the gumma is usually more rich in cells and undergoes in part a suppuration or cheesy necrosis (Fig. 492, d_2), while in other portions, particularly the peripheral, granulation tissue (*d*) and later connective tissue (d_1) are developed. The gumma occurs particularly in the periosteum (Fig. 493) and membranes of the brain (Fig. 492), as well as in the parenchymatous organs of the abdomen, especially in the liver (Fig. 494, *a*, *b*), spleen, and in the testicles.

In the meninges of the brain and spinal cord syphilitic inflammations lead in part to cicatricial thickenings and in part to the formation of encapsulated caseous masses. Periosteal syphilis, which occurs most frequently in the flat bones of the skull-cap (Fig. 493), and often in the facial bones, and the great long bones (the tibia), and may extend over the greater part of the skeleton, shows likewise the character of a granulomatous inflammation which leads to the formation of scar-tissue and new bone, so that osteophytes or hyperostosis may result. The severe forms, as represented by the formation of gummata, have a destructive action upon the bones and lead to caries and necrosis. The fresh inflammatory focus appears as a gray translucent, yellow or grayish-white pus-like focus surrounded by hyperæmic tissue, having its seat in the periosteum from which it may also extend to the marrow. The yellowish foci consisting of masses of small cells (Fig. 493, *c*) may die, the cells losing their nuclei (*d*), and in such places necrosis of the bone may also result. In living periosteal and endosteal tissue there occurs a new-formation of connective tissue (*e*, *f*), which, with the formation of multinucleated osteoclasts (*g*) and the formation of Howship's lacunæ, leads to destruction of the bony trabeculæ. In the case of a healing of the process this connective tissue may be again changed into bone.

In the liver the syphilitic lesions lead to the formation of radiating connective-tissue scars (Fig. 494, *b*, *c*, *d*), which often enclose cheesy remnants of the original inflammatory focus (*a*), that is, a caseous gumma. The process is similar in the other organs, for example, in the testicles and in the spleen.

The disintegration of syphilitic foci of the skin and subcutaneous tissue, as well as of the mucosa and submucosa, leads to the formation of **ulcers**, which, in the case of the mucous membranes, occur most frequently in the region of the mouth, throat, and the upper respiratory

tract (Fig. 495, [illegible]). In the neighborhood of the ulcers arising in mucous membranes there are not infrequently formed papillary proliferations (Fig. 495, [illegible]).

The cause of the frequent disintegration and necrosis occurring in syphilitic inflammations lies in the peculiar character of the exciting cause of the disease. A second factor may also be largely responsible for this manner of termination—namely, the extensive participation of

Fig. [illegible].—[illegible] [illegible] connective tissue with [illegible] of liver tissue; [illegible] connective-tissue bundle [illegible] liver tissue; [illegible] cellular [illegible] at the edge of the [illegible] nodule; [illegible] cellular [illegible] within the connective-tissue [illegible]; [illegible] liver tissue. [illegible]

the blood-vessels, particularly of the arteries, in the inflammation. When a syphilitic inflammation leads to the formation of granulation tissue or to a connective-tissue hyperplasia, the vessel-walls also become thickened, particularly the intima (Fig. 492, [illegible]), so that the vessel lumen is narrowed and not infrequently completely closed. Occasionally the syphilitic process is localized chiefly in the vessels.

Besides the peculiar foci of inflammation which point to a localization of the exciting cause of syphilis, there not infrequently occur in individuals who have suffered a syphilitic infection specific degenerations of the central nervous system (tabes, progressive paralysis), which are associated with proliferations of neuroglia. Nevertheless, these affections, though regarded as the *sequelæ of syphilis*, present histologically no peculiarities characteristic of syphilis, and occur in the same form in individuals who have never had a syphilitic infection.

Hereditary syphilis is characterized chiefly by peculiar tissue-changes which differ considerably from the manifestations of acquired syphilis, but changes also occur which correspond to the latter. In the skin hereditary syphilis may cause macular, papular, and pustular syphilides which may lead to ulceration. The liver, kidneys, adrenals, [illegible]

he bones may show circumscribed necrotic foci or inflammatory cellular infilrations. The spleen is usually more or ess enlarged, and in individual cases nay attain ten times its normal volume. n the liver there occur intravascular nd perivascular collections of round ells which often collect in small closely acked foci; associated with these there s a periportal new-formation of conective tissue. There is also a diffuse yperplasia of connective tissue throughut the entire liver (Fig. 496, *a*, *b*), giving to the organ a firm consistence and peculiar yellowish-brown color. Furher, there is also a proliferation of conective tissue limited to the periportal issue. The lungs may present, throughout or in part, a dense gray or grayishvhite structure resembling that of saroma tissue. This appearance is due to he formation in the altered area of a ellular connective tissue (Fig. 497, *a*,) which contains only imperfectly deeloped alveoli (e, e_1) and bronchi (d, d_1) or none at all. In cases of slight everity there exists only a thickening of the peribronchial and perivascular issue and interalveolar septa, in part associated with an accumulation of desquamated epithelium in the alveoli. In the kidneys and testicles the supporting connective tis-

FIG. 495.—Syphilitic ulceration of the larynx. Sagittal section through the larynx and trachea. *a*, Ulcer; *b*, thickenings and papillary proliferations on the epiglottis; *c*, thickenings and papillary proliferations on the left wall of the larynx and the superior thyro-arytenoid ligament. Natural size.

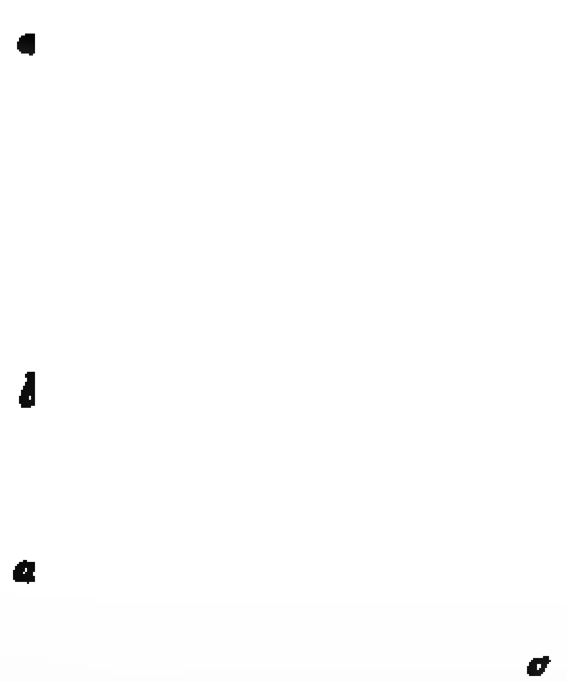

FIG. 496.—Induration of the liver in congenital syphilis (Müller's fluid, hæmatoxylin, eosin). *a*, Hypertrophic periportal connective tissue; *b*, indurated gland tissue infiltrated with connective tissue; *c*, collections of cells. × 100.

sue may likewise be increased in places, and abnormally rich in cells. *Syphilis also often causes in glandular organs a pathological development of the connective-tissue elements and collections of cells,* while the epithelial tissues are retarded in their development. In the blood the number of white corpuscles appears often to be increased. Finally,

d d e f

FIG. [illegible].—Changes in the lung in congenital syphilis. (Müller's fluid, hæmatoxylin, eosin.) *a*, Proliferating stroma rich in cells; *b*, cellular granulation-foci; *c*, artery with thickened adventitia; *d*, *d*$_1$, [illegible] bronchi, which in part (d_1) contain desquamated epithelium and round cells; *e*, *e*$_1$, alveoli, which in part (e_1) contain desquamated epithelium and round cells. × 32.

there not infrequently occur in the bones *disturbances of endochondral ossification*, which are characterized chiefly by irregularity in the formation of the medullary cavity and in the deposit of lime-salts in the cartilage, and lead to disturbances in the structure of the subchondral spongy bone-substance. Through the formation of granulation-tissue proliferations which undergo caseous necrosis, larger defects may arise in the bone substance.

It has been assumed by many authors that syphilis can be transmitted to the fœtus not only through the mother but also from the father through the sperm, and that the latter event can occur without the mother becoming infected with syphilis. *Matzenauer* opposes this view and declares that no clinical observations exist to exclude the transmission of lues through the mother. (See § 18.)

According to *Blaschko* (Berl. klin. Woch., 1908), Wassermann's "complement-binding" test for syphilis is reliable in that it never gives positive findings in the certain absence of syphilis. Complement is added to an inactive serum obtained from apes previously treated with organ-extracts or serum from a syphilitic man. After a certain time the serum thus treated is tested with an inactive specific hæmolytic serum and its corresponding red cells to see if the complement is wholly or partly anchored. Inhibition of hæmolysis occurs in the case of a serum resulting from [illegible] of syphilitic material.

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§ 173. The **Bacillus lepræ** (described by Neisser in 1879 and 1881, and by Armauer Hansen in 1880) is a small slender bacillus, from 4 to 6 μ long. It is regarded as the **cause of leprosy**—also called *elephantiasis Græcorum*. It is found constantly and in great numbers in the diseased tissues (Figs. 498, 499, 500)

The foci of disease in leprosy are in general characterized by a proliferation (Fig. 498) which consists of cells of different sizes and of a fibrous ground tissue. The bacilli lie sometimes between (*e*), sometimes in the cells (*c*, *d*), and in the latter appear usually in such great numbers that the cells may become greatly swollen (*d*) and in part become changed into mono- and multinuclear giant-cells (Fig. 499). The latter occasionally enclose large vacuoles which contain great numbers of bacilli as well as the granular, thready detritus of the liquefied protoplasm. The nuclei remain preserved for a long time, and are pressed to the pe-

riphery by the vacuoles containing the bacilli. Later they are destroyed, so that the entire cell becomes changed into a vacuole containing bacilli (Fig. 499). The cells in which the bacilli lie are in part the original cells of the tissue, and in part newly formed cells.

FIG. 498. FIG. 499.

FIG. 498.—Tissue from a leprous nodule (alcohol, fuchsin, methylene-blue). *a*, Fibrocellular tissue; *b*, round-cells; *c*, medium-sized cells; *d*, very large cells filled with bacilli; *e*, free bacilli. × [illegible].

FIG. 499.—Giant-cells, with vacuoles containing bacilli, from leprous proliferations of the nasal mucosa (alcohol, Gabbet's stain). × 400.

The bacilli are surrounded by a slimy envelope (Neisser), and react to stains in much the same manner as do tubercle-bacilli. The same staining methods may therefore be used for the former as for the latter. The stained bacilli often show clear spots or appear as if made up of stained granules.

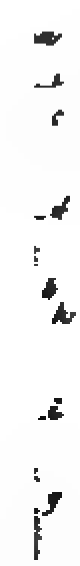

FIG. 500.—Section through a leprous nodule of the skin (alcohol, Gabbet's method). *a*, Epidermis; *b*, corium; *c*, hair-follicle; *d*, leprous focus in the neighborhood of the hair-follicle; *e*, duct of sweat-gland; *f*, leprous nodule about duct of sweat-gland; *g*, leprous foci in the neighborhood of sweat-gland; *h*, leprous focus having no especial relation with any of the specific skin structures; *i*, foci of bacilli. × [illegible].

Attempts to cultivate lepra bacilli have led to no important results, since the bacilli obtained in the cultures could not positively be identified as lepra bacilli. In the transplantation of leprous tissues into animals there occurs, of course, a transplanting of the bacilli, but the latter do not multiply and no progressive disease results.

The infection of man takes place by a direct or indirect transfer from individual to individual. The nasal secretion is especially infectious (Sticker), particularly when leprous suppurations are present in the nose. In the case of leprous affections of the respiratory tract the sputum may contain bacilli; and in the formation of nodules and ulcers in the skin the secretions from the latter may also contain the bacilli. Contagion seems to result most frequently from the nose (Sticker); in favor of this view speaks the fact that the anterior nasal region is usually involved very early. The bacilli are spread throughout the body chiefly by the lymphatic system; but they may also get into the blood-stream.

Besides the nose, the skin and the peripheral nerves are chiefly concerned in the disease; but the bacilli may multiply in other tissues, as

FIG. 501.—Leontiasis leprosa. (After G. Münch.)

in the testicles, liver, in the ganglia, and in the spleen, thereby giving rise to foci of disease in the organs.

At the place of colonization the bacilli excite inflammation with tissue-proliferation. Granulation tissue containing blood-vessels is formed; this remains for a long time in a condition which is characterized by great richness in cells, and forms the basis for nodules and tumors in

the skin and nose and for spindle-shaped thickenings of the nerves, and is the cause of the irritation and later of the degeneration and destruction of the nerve-fibres. The bacilli and the tissue-proliferations caused by their multiplication often group themselves in the skin about the hair-follicles (Fig. 500, *d*), the ducts (*f*), and the coil (*g*) of the sweat-glands, but such a relationship is not always to be seen (*h*). Moreover, the bacilli may penetrate into the blood-vessels, the hair-follicles, and sweat-glands (Tonton), and thence on to the surface of the skin. Infec-

FIG. 502.—Lepra anæsthetica ulcerosa of the leg and foot. (After G. Münch.)

tion of the arterial walls causes a proliferating arteritis, by which the walls become greatly thickened and the lumina narrowed. In the nervous system the bacilli are found both in the connective tissue and in the nervous elements, particularly in the ganglion cells (Sudakewitsch). The cells occupied by them undergo degeneration in the course of time, occasionally with hydropic swelling and the formation of vacuoles.

The tissue-proliferations caused by the growth of the bacilli may almost wholly disappear through the disintegration and absorption of the cells after the condition has lasted for years; but there always remain indurations rich in cells and pigmentations in the skin. Caseation never takes place.

Leprosy of the skin occurs especially in the face, on the extensor surface of the knees and elbows, as well as on the back of the hands and feet. It begins with the formation of red spots which either vanish, leaving pigmented spots behind, or become elevated into nodules of a brownish-red color (*lepra tuberosa sive tuberculosa sive nodosa*). In the region of the red spots the tissue contains large numbers of bacilli (Philipson), which for the most part lie within the vessels, and already at this stage the proliferation of the tissue can be demonstrated. According to the investigations of Müller the vesicular eruptions which occur in leprosy, and were formerly regarded as the sequelæ of the leprous disease of the nerves, are caused by the presence of the bacilli.

The nodules may remain unchanged for months, or they may increase in size and become confluent, so that very large protuberances may be formed, which, because of the distortion of the face thereby occasioned, have given occasion for the designation *facies leontina* (Fig. 501).

Through *external influences* ulcers may be produced which show no tendency to healing. New nodules appear occasionally following erysipelatous reddenings and swellings of the skin. The glands of the submaxillary and inguinal region swell to form very large nodules.

Leprosy of the nerves (*lepra nervorum sive anæsthetica*) leads first to

hyperæsthesia and pain, later to anæsthesia, more rarely to motor paralyses in the region of the affected nerves. The further consequences of the disease of the nerves are disturbances which express themselves in the skin by the formation of white and brown spots (*lepra maculosa, maculo-anæsthetica, morphœa nigra et alba*), and in the bones and muscles by atrophy. Since those suffering from the disease are likely to injure themselves after the appearance of anæsthesia, ulcers are often formed at a later period (Figs. 502, 503) which cause deep erosions and may lead to the loss of entire phalanges (*lepra mutilans*).

Leprosy of the skin and of the nerves are usually combined; more rarely do they occur alone. Besides the nose, skin, and nerves, the cen-

FIG. 503.—Lepra anæsthetica mutilans. Partial destruction of the fingers; ulcers in the hand. (After G. Münch.)

tral nervous system, mucous membranes, cornea, the cartilages, liver, lungs, spleen, lymph-glands, and the testicles, become diseased.

In Europe leprosy is confined mainly to Norway, Sweden, Finland, the Baltic Sea provinces of Russia, and the coasts of the Mediterranean; but occurs sporadically in other regions. It occurs very frequently in Hindustan, China, Sumatra, Borneo, Java, and Mexico, on the northern and eastern coasts of South America, in Upper and Lower Guinea, in Cape Colony, and on the northern coast of Africa.

Leprosy is prevalent in Mexico, the West Indies, and in the Philippines, and cases are found in New Brunswick and other parts of Canada. Cases are also scattered throughout the United States, the most important centres being in Louisiana, Califor-

na, and Minnesota. According to a Senate report of 1902, there were at that time 278 known cases of leprosy within the borders of the United States.

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§ 174. The **Bacillus mallei** is a bacillus discovered by **Löffler, Schütz** and **Israel** in glanders foci, and later confirmed and studied by **Weichselbaum**, Kitt, and others. It is to be regarded as the **cause of glanders** (*malleus, malleusmus*) and of *farcy* (*skin glanders, malleus farciminosus*), a contagious disease of horses, which occurs in man chiefly through transmission from horses.

The glanders bacilli are very small, slender rods, which occur in the diseased foci, sometimes scattered, sometimes lying together in small clumps. Alkaline methylene-blue or gentian-violet is employed especially for their staining.

The bacilli are present chiefly in the glanders-foci, but at times appear in the blood of the affected individual (Löffler, Kitt).

The bacilli grow at a temperature of 30°–40° C., upon coagulated blood-serum, as well as upon slices of boiled potato, and upon potato-pap. Upon the latter they form amber-yellow coatings that later become red. Upon blood-serum they form small yellowish transparent drops which later become milky white. Upon agar the colonies are grayish-white. In cultures club-shaped forms and threads are not infrequently seen. Spore-formation has not been demonstrated.

Horses, asses, sheep, young dogs, goats, cats, guinea-pigs, and field-mice are suitable for inoculation. In cats, after inoculation, there develop in the testicles cellular foci consisting essentially of leucocytes

FIG. 504.—Glanders of a cat's testicle (Müller's fluid, hæmatoxylin). *a*, Seminiferous tubules; *b*, *c*, tubules filled with leucocytes; *d*, foci of leucocytes in the connective tissue. × 90.

(Fig. 504), which lie partly inside the canaliculi (*b*, *c*) and partly around them (*d*). The injection of the pus of glanders into the peritoneal cavity of male guinea-pigs causes the testicles to swell rapidly (Straus). After subcutaneous inoculations ulcers develop at the seat of inoculation, followed by swelling of the neighboring lymph-glands. Later, nodules may develop in the internal organs, and ulcers may be formed in the nose. Typical glanders may be produced in horses and asses. Cattle, white mice, and house-mice are immune.

The usual atrium of infection in horses is the mucous membrane of the nose; following this is the involvement of the submaxillary glands, and further a metastasis in various organs. In the nasal mucosa there

arise as the result of the infection either diffuse cellular infiltrations of the mucosa or subepithelial nodules of the size of a millet-seed or a pea. In chronic farcy of the skin larger nodules are developed which join together in rows, forming worm-like cords.

The nodules of the mucous membrane break down easily. The cells of which they are composed bear for the greater part the character of pus-corpuscles. Through the disintegration, softening, and suppuration of the nodules ulcers with yellowish infiltrated bases are formed. These enlarge through a progressive, nodular or more diffuse infiltration and subsequent disintegration of the edges of the ulcer, as well as through the confluence of neighboring ulcers. Horses dying of glanders often present in the mucosa of the nasal septum very extensive irregularly shaped, sinuate ulcers, with eroded edges and floors covered with gray and yellowish material. In addition to these there are numerous small, lenticular ulcerations and gray or yellowish nodular foci which are on the point of breaking down. The whole process is closely related to purulent inflammation. The healing of the ulcer is characterized by the formation of radiating scars.

The cervical lymph-glands are constantly swollen and inflamed. Of the internal organs the lungs especially are involved. They contain either nodules having a caseated and disintegrated centre and a grayish cellular periphery, or foci of lobular pneumonia, which present either a clear gray or a more hæmorrhagic appearance, or through fatty and cheesy metamorphosis become opaque and yellowish-white. Occasionally the mucosa of the alimentary tract contains nodules of varying size, in part clear gray and consisting of cellular tissue, in part opaque yellowish-white, undergoing caseation or approaching suppuration. The spleen, liver, kidneys, and bone-marrow may also contain nodules.

In farcy, which runs a more chronic course than glanders, there are formed in the skin and muscles nodules consisting of a small-celled tissue which later undergoes retrogressive metamorphoses, caseates and disintegrates.

In **man an infection with glanders** takes place usually through small wounds of the skin, but may also occur primarily in the mucous membranes adjacent to the skin. In the skin and subcutaneous tissue it gives rise to roseolar spots, hæmorrhages, and papular, nodular, and pustular exanthemata, carbuncular and phlegmonous inflammations which may result in suppuration, and to purulent inflammations of the lymph-vessels and lymph-glands. In the mucosa of the respiratory tract catarrhs are produced and suppurating nodules and nodes are formed, leaving ulcers behind. In the internal organs metastatic small-celled nodules are formed, showing a tendency to suppuration; also extensive abscesses and purulent infiltrations, especially in the muscles. In chronic farcy which may last for years, large nodules are occasionally formed in the skin and muscles which through disintegration give rise to ulcers which heal with difficulty. For the diagnosis of the condition the bacteriological examination and inoculation experiments are necessary.

According to the investigations of *Kalning*, *Preusse*, and others, an active poison, *mallein*, may be extracted from cultures of glanders bacilli, which, when injected in small doses into horses sick of glanders, causes a febrile rise of temperature, and may be used as a diagnostic aid.

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§ 175. As the **Bacillus of rhinoscleroma,** Frisch, Pellizari, Chiari, Cornil, Alvarez, Köbner, Paltauf, von Eiselsberg, Dittrich, and others have described a bacillus with rounded ends, which is constantly present in the diseased condition known as *rhinoscleroma* or *scleroma respiratorium* (Bornhaupt, Wolkowitsch), and is therefore regarded as the cause of the same. It stains best with methyl-violet, the sections being left in the stain for twenty-four to forty-eight hours. After staining, the sections are treated with iodine water, or left in absolute alcohol for one to three days. The bacilli, for the greater part, possess a hyaline capsule and are closely related to the pneumonia-bacillus (§ 166).

Rhinoscleroma occurs chiefly in eastern Austria and southwestern Russia; isolated cases have been observed also in Silesia, Italy, Egypt, Belgium, Sweden, Switzerland, and Central America. It is a chronic disease progressing for years, beginning in the nose (Wolkowitsch), more rarely in the pharynx, larynx, or palate, and extending thence to neighboring parts—the external nose, lips, lachrymal duct, trachea, etc. In

the nose the disease is characterized by a thickening of the nasal walls which is sometimes diffuse, sometimes elevated or nodular. The external skin takes on a red or brownish-red color, becomes stiff and fissured and covered with scales. In the throat and respiratory tract dense, cartilage-like infiltrations are sometimes present, at other times a contracting cicatricial tissue is formed. The infiltrations may appear in the form of nodes and nodules or as elevations and flattened areas of thickening, or they may be spread out more diffusely. By the transformation of the infiltration into scar tissue marked deformities of the

FIG. 505.

FIG. 506.

FIG. 505.—Section of rhinoscleromatous tissue, with numerous degenerated and vacuolated cells containing bacilli (osmic acid, hæmatoxylin). Preparation by Stepanow. × 340.

FIG. 506.—Cells in condition of hyaline degeneration, and hyaline spherules, from rhinoscleromatous tissue of the vocal cord and of the nose. Preparation by Stepanow. *a*, *b*, *c*, *d*, Hyaline-degenerated cells containing small bacilli; *e*, hyaline cells with encapsulated bacilli; *f*, *g*, cells with hyaline spherules; *h*, free hyaline spherules. *a*, *b*, *c*, *d*, Stained with Löffler's solution; *e*, with hæmatoxylin; *f*, *g*, *h*, with fuchsin. × 425.

affected organs may be produced. Deep destruction of the tissues is absent; superficial ulcerations may, however, occur. On section the infiltrated tissue appears yellowish, spotted, but not infrequently shows a gray or grayish-red color. The tissue of the affected areas consists partly of granulation tissue, partly of fibrous connective tissue. If the former extends to the epithelial covering there appear in part proliferations, in part degenerative processes in the epithelial cells, the latter being characterized by the formation of vacuoles and by an infiltration of the part with round cells. According to Stepanow the vacuoles may contain bacilli.

The granulation tissue itself shows in many places no especial peculiarities; rather does it present the same conditions present in other inflammatory infiltrations and proliferations of connective tissue. In other places, on the contrary, there may be found a larger or smaller number of large connective-tissue cells containing one vacuole or showing a total vacuolar degeneration or a reticulated structure, in the meshes of which bacilli may be demonstrated (Fig. 505), some of the latter possessing capsules.

Besides the cells showing vacuolar degeneration there also occur cells of various shapes which have undergone hyaline change (Fig. 506, *a*, *b*, *c*, *d*, *e*). These also contain bacilli with and without capsules, and also coccus-like forms. Through the loss of their nuclei these cells may become converted into non-nucleated homogeneous lumps (*d*). Finally, there also occur cells which enclose hyaline spherules (*f*, *g*), and free spherules are also found lying in the tissues (*h*). In places not yet af-

fected by cicatricial retrogression the hyaline formations may be present in large numbers.

According to *Paltauf*, *von Eiselsberg*, *Dittrich*, *Wolkowitsch*, and others, the bacilli of rhinoscleroma may be cultivated upon blood-serum, gelatin, agar-agar, and potatoes, and also form capsules in the cultures. When grown in bouillon they show on the contrary no capsules (*Dittrich*). Stab-cultures in gelatin resemble closely the nail-cultures of the Friedländer pneumonia-bacillus, but are of a translucent grayish-white and not dead white. The bacilli stain more easily than the pneumonia bacilli, and also stain by Gram's method. *Stepanow* observed, in inoculations into the eyes of guinea-pigs, progressive inflammations and proliferating granulations containing the bacilli and hyaline degenerated cells.

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§ 176. The **Actinomyces** or **ray-fungus** is a polymorphous fission-fungus which appears in different forms of growth in the human and animal organism as well as in cultures. It is the cause of **actinomycosis**, a disease occurring in man as well as in cattle, swine, and horses, more rarely in sheep, dogs, and cats, and characterized by a progressive inflammation that produces in part granulation tissue and connective tissue, and in part pus. The botanical position of the fungus is still unsettled. By many it is classed with the *thread-fungi*, others group it with the *polymorphous bacteria*. Boström places it in the group *cladothrix;* Kruse, in the group *streptothrix*.

According to the investigations of Boström actinomyces differs from the bacilli in the fact that in cultures upon beef's-blood serum or agar it forms *branching threads.* The threads of the cultures are partly straight, partly wavy, at times also twisted spirally. They break up by transverse division

FIG. 507. FIG. 508.

FIG. 507.—*Actinomyces hominis.* Teased preparation. × 700.

FIG. 508.—Actinomycosis of the tongue (alcohol, alum carmine.) *a*, Actinomyces druse; *b*, *c*, cellular nodules; *d*, transverse section of muscle; *e*, *f*, connective tissue with blood-vessels. × 1??.

into short rods and coccus-like forms, which under suitable conditions again grow into threads.

Within the human and animal organism the fungus appears in masses in the form of little granules scarcely recognizable by the naked eye, or

FIG. 509.—Actinomyces druse, surrounded by epithelioid and pus-corpuscles (alcohol, hæmatoxylin, eosin). *a*, Fungus druse; *b*, mononuclear and multinuclear epithelioid cells; *c*, pus-corpuscles; *d*, phagocyte, enclosing a pus-corpuscle; *e*, granulation tissue. × 500.

in spherules up to 2 mm. in diameter. These are sometimes colorless and transparent, at other times white and opaque, sometimes yellow, or brown, or green and yellowish-green. Many of the smaller ones consist

only of a feltwork of fine, partly branched threads, some of which are straight, or wavy, or twisted. The majority of the granules contain, moreover, peculiar club-shaped structures (Fig. 507), which form the ends of the threads, and if present in large numbers, as is the case particularly in the larger granules, have a radial arrangement (Figs. 508, *a*; 509, *a*), and so give to the colony of the fungus a ray-like appearance. Occasionally band or fan-like forms develop on the ends of the threads. According to Boström, all these peculiar structures are due to a swelling

FIG. 510.—Actinomycosis of the lung (alcohol, carmine, Gram's). *a*, Fungus druse; *b*, small-celled nodule; *c*, fibrous tissue; *d*, alveoli filled with large and small cells; *e*, bronchiole with wall infiltrated with cells; *f*, small-celled focus in the neighborhood of the bronchus (*e*); *g*, alveoli filled with vascularized connective tissue; *h*, connective tissue growing into the alveoli; *i*, blood-vessels of the lung tissue; *k*, blood-vessels of the inflamed area. × 42.

of the membrane of the threads, and are to be regarded as retrogressive changes.

The actinomyces is usually taken into the body with the food or the respired air, and finds its first development often in the mouth. The fungus has not yet been demonstrated outside of the human and animal organism. It must be remarked that very often bits of higher plants (beard of wheat, splinter of wood, a bit of grass) have been found in the pus of actinomycotic foci, and that the swallowing of portions of plants (spike of grain [Bertha]) or the contamination of wounds with vegetable material, have in certain cases preceded the development of actinomycosis. It is, therefore, very probable that the fungus is present upon the higher plants or upon wood. Johne demonstrated it as early as 1882 upon beards of wheat found sticking in the tonsils of swine. Ac-

cording to Bang, it develops also upon wheat grains and straw. If beans, rye, or barley is grown in a soil infected with actinomyces cultures (Liebmann) the ray-fungus may be found later in various portions of the plants.

If the ray-fungus succeeds in settling in a tissue it excites an inflammation in its neighborhood. While the fungus which has penetrated into the tissue develops a mycelium and a fungus-granule (Figs. 508, *a*; 509, *a*; 510, *a*) there is formed in its neighborhood a nodular focus of inflammation, which at first consists of leucocytes (Figs. 508, *b*, *c*; 510, *b*); but later, in addition to pus-corpuscles (Fig. 509, *c*), also contains epithelioid cells and giant-cells (*b*, *d*).

The fungus-granules may increase within the nodule and lead to its enlargement; and it very often happens that cellular nodules the size of a pea and larger contain a large number of fungus-foci, which are usually situated in the periphery of the same. At the same time new fungus-foci, and consequently new cellular foci, may appear in the neighborhood. The further spread of the infection takes place by means of small rods and threads, which are broken off from the larger masses, and may be seen in the tissues partly free and partly enclosed in cells.

FIG. 511.—Frontal section through the nose and upper jaw of a steer affected with a tumor-like actinomycosis. *a*, Nodules consisting of connective tissue, bone, and small pus foci. One-fourth natural size.

Larger nodules often undergo in time a purulent liquefaction of their central portions, leading to the formation of small *abscesses*, which may become confluent to form larger *pus-cavities* or *sinuses*. In the neighborhood of the purulent areas (Fig. 510) there develops early an active *proliferation of tissue*, which leads to the *formation* of *vessels* (*k*) and young *granulation tissue*, which later becomes transformed into cicatricial *connective tissue* (*c*, *g*, *h*). If the connective-tissue proliferation attains very considerable proportions, it leads to an *induration* (Fig. 510), often also to an *enlargement of the tissue*. The connective-tissue proliferation may finally extend into the small-celled areas, and replace the latter, the fungi probably being destroyed in this way.

A predominance of tissue-necrosis and of suppuration over tissue-production gives rise to more or less extensive sinuous cavities and branching fistulous tracts communicating with one another. The walls of these consist of granulation-tissue and hyperplastic connective tissue, and here and there contain fungus-foci. The masses of fungi may in part become calcified.

In cattle the disease affects chiefly the lower jaw, but may involve also the upper jaw (Fig. 511, *a*), the tongue, throat, larynx, œsophagus, stomach, intestinal wall, skin, lungs, and subcutaneous and intermuscular tissues; in *swine* it is found in the udder and different bones of the skeleton, while in *horses* it occurs chiefly in the vas deferens following castration. In cattle it leads to the formation of more or less extensive fibrous tumors containing purulent foci, and was formerly given various

names, such as osteosarcoma, bone-cancer, bone-tuberculosis, lumpy jaw, wooden tongue, tuberculosis of the tongue, lymphoma, fibroma, worm-nodules, etc.

In *man* the infection, so far as is known, takes place through the mouth, fauces, œsophagus, stomach, intestine, and lung, or through some external injury. In the first-named region an infection of actinomyces may take its start from carious teeth (cavities or fistulæ), or from any injury to the soft parts of the jaw or cheek. Thence it spreads over the neighborhood and may finally involve the face and the hairy portions of the head, as well as the throat, neck, back, and breast.

With the advent of the process there arise swellings which later soften and give fluctuation. When the latter is the case, pus is formed which is at times thin and watery, at other times more viscid, and contains the characteristic granules. If these abscesses break externally there may be formed fistulous tracts, which may either close again, or continue to secrete pus.

Besides these purulent foci, which sometimes are small, at other times extensive, there is constantly formed more or less granulation tissue, which at times may be very abundant. As a result of fatty degeneration and disintegration of its elements the granulation tissue often becomes partially whitish or yellowish or reddish-white in color, and permeates the diseased tissue in an irregular manner. In other places it comes to a development of connective tissue, particularly in those places where the process is not spreading.

Through this development of connective tissue a local healing resulting in cicatricial indurations may take place, but in other parts the process usually makes further progress and may under certain circumstances lead to very extensive destruction. If the disease encroaches upon the bones of the spinal column or of the thorax these may be gradually destroyed from the surface, and become rough, eroded, and carious. In rare cases the jaw-bone may be attacked from within through an alveolar process, and so undergo destruction. From the base of the skull the process may extend into the interior of the skull and lead to actinomycotic meningitis and encephalitis.

In primary infection of the respiratory apparatus the process takes the form of a bronchopneumonia characterized by the formation of nodular foci (Fig. 510, *b*) the central portions of which at an early stage assume a yellowish-white color. Through the disintegration of the inflammatory foci cavities may be formed which contain fluid, pus-corpuscles, fatty detritus, spherules of fatty granules, disintegrated red cells, and masses of actinomyces. The tissue lying between the mycotic foci suffers a more or less extensive, often very marked, inflammatory thickening and induration (Fig. 510, *c*), and through a new-formation of connective tissue may be transformed into a callous, slate-gray or gray and white mass, devoid of air, and later undergoing cicatricial contraction. In this manner a large portion of the lung may become converted into a mass of connective tissue.

From the lung the process sooner or later extends to the visceral pleura, and from this to the costal pleura or to the pericardium, giving rise in these places to inflammatory exudations and proliferations of tissue, which may lead to adhesions between the opposite layers of the pleura or pericardium. From the costal pleura the cellular infiltration as well as the pus formation and the fatty degeneration and disintegra-

tion of the granulation tissue may extend between the ribs to the outside, and spread in the contiguous soft parts, in the connective tissue and muscles, and may finally break through in places. From the lungs a rupture may sometimes take place into the mediastinum or pericardial sac, and finally into the heart. Under certain conditions a rupture may occur through the diaphragm into the abdominal cavity, or the process may extend from the posterior mediastinum into the retroperitoneal connective tissue.

The secondary areas of destruction lying outside of the lung often reach an extremely large size, while in the lung the primary process advances but little and undergoes cicatrization. At one time the purulent softening predominates, at another time the formation of granulation tissue and the induration.

Primary actinomycosis of the intestinal tract begins with the formation of plaque-shaped whitish patches of the fungus (Chiari) or of nodular mucosal and submucosal foci (Zemann), which contain the specific fungus, and lead to ulceration through the occurrence of disintegration. From the intestine the process spreads over the peritoneum and the retroperitoneal connective tissue, as well as to the organs adjacent to the primary focus—for example, the liver; and may finally break through the abdominal wall.

Metastasis may be associated with the local progression of the disease, but is rather rare. It usually results from a direct rupture into a blood-vessel. The metastases arising from a primary focus in the intestine are found especially in the liver; those arising from a primary focus in the lungs are found in the skin, muscles, bones, brain, intestine, and kidneys. The metastatic nodules behave like the primary foci. In rare cases there occur also primary foci of actinomycosis in the internal organs—for example, in the brain and liver. The portal of entrance in these cases may not be demonstrable.

Johne, Ponfick, Boström, Wolff, and Israël have attempted inoculation experiments upon animals, and according to their reports have obtained positive results in part (Johne, Ponfick, Wolff, and Israël). Wolff and Israël, by the inoculation of rabbits and guinea-pigs, obtained in almost all cases a characteristic disease with the formation of inflammatory foci containing the fungus-masses. They were also able again to cultivate upon agar-agar the fungus contained within these foci.

Levy, as well as *Kruse*, assumes that there are two forms of actinomyces, an aërobic cultivated by *Boström*, and an anaërobic cultivated by *Wolff, Israël, Aschoff*, and himself, the two forms being closely related. *Mertens* announces that he has succeeded in changing the Wolff-Israël form into the Boström. Levy regards the actinomyces as well as the fine-threaded fungus known as *streptothrix* as belonging to a group, the *Hyphomycetes*, characterized by the formation of branching, probably unicellular mycelia and which multiplies through an acrogenic snaring-off of conidia-chains or through fragments of threads resembling bacilli. Since the ray-fungi do not correspond to any one of the known hyphomycetes-groups, he places them in a separate group, the **Actinomycetes.** In this group he also places the tubercle-bacillus, the lepra-bacillus, the diphtheria-bacillus, and the bacillus of glanders. *Lubarsch* regards the streptothrices, with which he classes the ray-fungi (to which the tubercle-bacillus also belongs), as a transition form between the bacilli and the moulds.

Berestnew also distinguishes different forms of actinomyces (cultivated by him from straw, hay, etc.), and, in addition to *actinomycosis*, recognizes a condition of *pseudo-actinomycosis*, which runs a similar course to that of the former, but is caused by fungi which do not belong to the ray-fungi. *Kruse* and *Gilbert* likewise regard the etiologic factor of an actinomycosis as being of varied nature and not representing a definite entity. *Schürmayer* emphasizes the variability of actinomyces according to the conditions of growth. *Wright* believes that human and bovine actinomycosis are identical, and

further holds that there is but one species of microorganism (*Actinomyces bovis*) concerned in the production of typical actinomycosis. The lesions produced by other forms of branching organisms he would class under the head of *nocardiosis*, reserving the term actinomycosis for those conditions in which characteristic " drusen " are formed.

According to *Dunker* (*Zeitschr. f. Mikroskopie und Fleischschau*, iii., 1884) and *Hertwig* (*Arch. f. wissensch. u. prakt. Thierheilk.*, xii., 1886) there occurs in *hogs* a *ray-fungus* which is always situated in the muscles, particularly in the diaphragm, abdominal and intercostal muscles, and causes a degeneration of the muscle-fibres in its neighborhood and proliferation of the intermuscular connective tissue. The fungus-masses form radially arranged clubs. They readily undergo calcification and then form white points in the flesh.

Petruschky unites Actinomyces, Streptothrix, Cladothrix, and Leptothrix into one family, which he calls the **Hair fungi** or **Trichomycetes.** These he classes also with the hyphomycetes, of which he distinguishes two great classes, the mould fungi and the hair fungi.

Actinomyces is characterized by radiating forms; *streptothrix* by true branching, late fragmentation of the wavy threads and the formation of conidia; *cladothrix* by false branching of the threads (a lateral direction of the membrane with a continuation of the longitudinal growth in the other direction) and rapid fragmentation of the threads; while *leptothrix* is characterized by stiff threads without branching.

There occur numerous observations in which organisms apart from the actinomyces described above and belonging to the **trichomycetes,** particularly to the *streptothrices*, gave rise to local tissue-changes, particularly purulent and granulating inflammations, and in part also to tubercle-like changes, but in many cases the authors have not agreed as to what species the fungus concerned belonged.

As early as 1855 fungus masses were observed by *von Graefe* in the inflamed lachrymal duct. These were at first regarded as favus, but later *Cohn* (1874) regarded them as streptothrix and gave them the name of *Streptothrix foersteri*. Likewise *Axenfeld*, who has many times cultivated the fungus, regarded it as a variety of streptothrix.

Under the term *Cladothrix asteroides Eppinger* has described a polymorphous fission fungus or hair fungus found in the pus of an old cerebral abscess causing death through meningitis. Since in the affected individual changes similar to tuberculosis were found in the lungs and bronchial glands and since inoculation of guinea-pigs and rabbits gave rise to a disease resembling tuberculosis, he has designated the disease produced by the fungus as *Pseudotuberculosis cladothrichica*. *MacCallum* regards Eppinger's fungus which he obtained from a purulent peritoneal exudate as belonging to the Actinomyces group and calls it *Actinomyces asteroides*. *Schabad* regards a fungus characterized by branching threads which he found in a subpectoral abscess, and according to its behavior in cultures apparently identical with the Eppinger fungus, as belonging to the actinomyces group, and designates it an atypical actinomyces which differs from the typical form in that it produces no clubs and is acid-fast. In animals it causes a pseudotuberculosis.

Buchholtz found a variety of streptothrix in a pneumonic lung containing large cavities of disintegration, with ragged walls. *Langer* found a streptothrix pathogenic for guinea-pigs in the sputum of a thirteen-year-old boy, which probably arose from an œsophageal diverticulum.

According to investigations by *Kanthack*, *Boyce*, and *Vincent* it is very probable that the disease occurring in India known as **Madura-foot** or **Mycetoma,** characterized by gradual swellings in the extremity, with nodular deposits becoming changed into abscesses and fistulous tracts through suppuration, and on pressure discharging purulent gray, or brown to black, fish-roe or trufflelike granules is caused by a polymorphous *fungus related to Actinomyces* and designated by *Vincent* as *Streptothrix maduræ*. *Kanthack* regards the fungus which is enclosed in the granules as identical with the Actinomyces, but the investigations of *Vincent* and *Boyce* do not agree with this assumption. According to *Boyce*, the *Streptothrix maduræ* occurs in two varieties, one white or yellow, with fine dichotomous branching threads and one black, with branched pigmented threads. *Unna* and *Delbanco* also distinguish different fungi which they class with the Actinomyces. According to *Oppenheimer* mycetoma is a granuloma with abscess formation caused by two kinds of fungi; the yellow form is an actinomyces, while the fungus of the black form cannot at the present time be exactly classified, but probably belongs to the oïdia or moulds. The parasite of the madura disease has been known since the year 1874 (*Carter*, *Lewis*, and *Cunningham*), and was formerly called *Chionyphe Carteri*.

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For literature on Streptothrix, Cladothrix, and Leptothrix see facing page.

§ 177. In addition to those already described there is a large number of **bacilli pathogenic for animals** which may also cause infection in man. The most important animal diseases caused by bacilli are symptomatic anthrax, swine-erysipelas, swine-plague, swine-pest, cattle-plague, and chicken-cholera.

The **bacillus of blackleg** or **symptomatic anthrax** (*Bacterie du charbon symptomatique, Clostridium sarcophysematos bovis*) is a rod with rounded ends about 3–5 μ long and 0.5–0.6 μ broad, and sometimes possessing independent motion. According to the investigations of *Bollinger*, *Feser*, *Arloing*, *Cornevin*, *Thomas*, and others, it is constantly found in blackleg.

Blackleg occurs particularly in young cattle and in lambs, and is usually fatal within two days. It is characterized anatomically by a tumor-like swelling of the skin

Literature.

(Streptothrix, Cladothrix, and Leptothrix.)

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due to the exudation of a bloody serous fluid attended by the formation of gas in the subcutaneous, intermuscular, and muscular connective tissue. The bacilli are found in the region of the exudation and gas-formation, as well as in the spleen and liver. They do not stain with Gram's method.

According to *Arloing*, *Cornevin*, and *Thomas*, the bacilli may be cultivated, in the absence of oxygen, in chicken-bouillon, to which a small amount of glycerin and sulphate of iron is added. *Kitasato* and *Kitt* cultivated them in guinea-pig bouillon, agar, and gelatin in the absence of oxygen. They grow best at from 36°–38° C., and form spores in the middle or at the ends of the rods, whereby the latter become somewhat swollen. The addition of sugar and glycerin to the nutrient medium aids the growth. The inoculation of cattle and sheep with bacilli which are attenuated by heating produces an immunity against virulent bacilli. Cattle, sheep, goats, rabbits, guinea-pigs, swine, dogs, cats, and chickens are susceptible to the bacilli of symptomatic anthrax; black rats are immune; horses and donkeys occupy an intermediate position.

The inoculation of guinea-pigs with virulent material—for example, with the dried juice of the muscle of cattle dying of blackleg—leads very quickly to a rapidly spreading swelling at the point of inoculation, due to the infiltration of the tissues with a bloody œdema. The bacilli spread with remarkable rapidity in the tissues, particularly in the subcutaneous and intermuscular tissue, and penetrate also into the muscles. They cause severe lesions of the vessels, leading to hæmorrhages and serous exudations, and after a time to an abundant emigration of leucocytes. The animals usually die on the second or third day after the swelling has spread over a portion of the body. The blood usually remains free from bacilli. Spores are not formed in the living body.

Literature.

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The **Bradsot Bacillus** is an anaërobic bacillus closely related to that of symptomatic anthrax. It forms spores and at times possesses numerous flagella, and causes the disease of sheep known as *Bradsot* or *Braasot*, which is found particularly in the northern portions of Europe. The sheep dying from the disease show a hæmorrhagic serous inflammation of the stomach, hæmolysis, and serous inflammation of the connective tissue, at times with gas formation (*Jensen*, "Bradsot." "Hand. d. path. Mikroorg.," ii., Jena, 1903).

The **bacillus of swine-erysipelas** (*Löffler*, *Lydtin*, *Schottelius*, and *Schütz*) is a bacillus from 0.6–1.8 μ long. It may be cultivated in bouillon, meat-infusion-peptone-gelatin, blood-serum, and sour milk at 18°–40° C.

In gelatin-plates it forms peculiar radiating and branched figures. In stab-cultures it grows out in white streaks from the stab-canal like the bristles of a test-tube brush. In cultures the bacilli may form pseudothreads. By means of pure cultures the disease may be reproduced in susceptible swine. House-mice and pigeons die within two to four days after inoculation, and their blood contains numerous bacilli.

In rabbits, inoculation is followed by an erysipelas-like inflammation which terminates either in a fatal general infection or in healing. Guinea-pigs and chickens are immune.

According to investigations by *Pasteur* and *Thuillier*, and confirmed by *Schottelius* and *Schütz*, the virulence of the bacilli for swine may be attenuated by progressive inoculations in rabbits. Susceptible swine inoculated with this vaccine do not die after inoculation and become immune to fully virulent bacilli.

Swine-erysipelas occurs particularly in young herds of highly-bred (English) hogs, while the common breeds are nearly or wholly immune. The disease is characterized by fever and the appearance of red spots, later becoming brown, upon the neck, chest, and belly. Intestinal hæmorrhages occasionally occur. More than half of the infected animals die, usually within a few hours or within four days. The autopsy shows swelling and localized hæmorrhages in the mucosa of the intestine, swelling and ulceration of the follicles, particularly in the ileocæcal region, swelling of the mesenteric lymph-glands, and petechiæ of the serous membranes.

The bacilli are found in the blood as well as in the lymph-glands, muscles, spleen,

and kidneys, where they also lie in the blood-vessels. The majority are free; some are enclosed in leucocytes. They are stained by Gram's method.

Literature.

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Löffler: Schweinerothlauf. Arb. a. d. K. Ges.-Amte, i., 1885.
Lorenz: Schutzimpfung gegen Schweinerothlauf. Cbl. f. Bakt., xv., 1894.
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Preisz: Rothlauf d. Schweine. Handb. d. path. Mikroorg., iii., 1903.
Schütz: Rothlauf d. Schweine. Arb. a. d. K. Ges.-Amte, i., 1885.

The **Bacillus suisepticus,** the cause of German swine plague or *swine septicæmia* (*swine plague* [Salmon]) is a bacillus discovered by Löffler in 1886. It is about 1.2–1.4 μ long and 0.4–0.6 μ broad. It is a facultative aërobe, grows easily upon the ordinary culture media, and when stained usually shows a polar staining while the middle portion remains clear. In natural infection the hogs may die within twenty-four hours from septicæmia and bacteriæmia. The bacilli may be found in all the organs. If the skin is the avenue of entrance there occurs at this point a subcutaneous inflammatory œdema. More frequent is the form known as *pectoral swine plague*, which occurs both in an acute and a chronic form. In the former there occur multiple croupous-hæmorrhagic bronchopneumonias that become gangrenous, and may be associated with a pleuritis, pericarditis, and peritonitis. In the chronic form, which is the most common in Germany, pulmonary hepatizations, with or without necrosis, are formed. In the majority of cases it is a bronchogenic pulmonary disease, but the infection may take place through wounds or the intestine and secondarily reach the lung. Hogs, mice, rabbits, and guinea-pigs are susceptible to inoculations; pigeons, chickens, and calves less so, and dogs and horses still less. The bacillus produces a local inflammation. If it passes from the lymphatics into the blood there occurs a marked increase of the bacilli, particularly in the lung and liver (*Joest:* "Schweineseuche und Schweinepest." "Handb. d. path. Mikroorg.," iii., 1903).

The **Bacillus of Swine Pest** or the *American Swine Plague (hog cholera [Salmon], swine plague [Billings], swine fever [Brown]).* the **Bacillus suipestifer** (*Bacillus choleræ suis [Smith]*), forms rods with rounded ends about 1.2–1.8 μ long and 0.6 μ broad. It does not stain by Gram's method. When stained with basic aniline dyes it shows in part a polar or peripheral stain. It may easily be cultivated on the ordinary media, is a facultative aërobe, moves by means of numerous flagella, and produces no spores. The plague is endemic in North America, and has been introduced thence into Europe. It occurs in two chief forms. The *septicæmic-hæmorrhagic* form is characterized by hæmorrhages in various organs, particularly the lymph-glands, serous membranes, intestine, and kidneys. In the *intestinal form,* which is more frequent, inflammatory changes are found in the intestinal tract, particularly in the colon, bearing in part the character of catarrhal or in part croupous, hæmorrhagic, and diphtheritic inflammation.

The infection takes place chiefly through the intestinal tract, where the most severe changes are found. Through the transportation of the bacilli through the lymph and blood changes in other organs are produced and a septicæmia or bacteriæmia. Mice, rabbits, guinea-pigs, and white doves are susceptible to inoculation; horses, sheep, and cattle are not killed by inoculation; local inflammations alone are produced.

Swine pest and *swine plague* may occur in the same individual as a *mixed infection,* and may infect whole herds. Such epidemics are characterized by great virulence.

Literature.

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Karlinski: Schweinepest und Schweineseuche. Z. f. Hyg., 28 Bd., 1898.

The **Bacillus of Mouse Typhoid** is a bacillus observed by *Löffler* in an epidemic of mice kept in the laboratory. House mice and field mice are very susceptible to it

It may be used as a means of extermination of field mice. (Löffler: "Epidemieen unter den im hyg. Institut. zu Greifswald gehaltenen Mäusen und über die Bekämpfung der Feldmauseplage," *Cbl. f. Bakt.*, xi. u. xii., 1892.)

The **bacillus of chicken-cholera,** or *avian typhoid*, or *bird septicæmia*, a disease occurring epidemically among chickens, is a small bacillus from 1–1.2 μ long, often somewhat constricted in its middle. It was first studied by *Perroncito*, then by *Toussaint, Pasteur, Rivolta, Marchiafava, Celli*, and *Kitt*. It does not stain by Gram's method. The disease is characterized clinically by great exhaustion and stupor, occasionally also by diarrhœal intestinal discharges; anatomically by swellings of the liver and spleen, hæmorrhages and inflammations of the intestine, and also frequently by pleuritis and pericarditis.

The bacilli are found in the blood and therefore also in the capillaries of the different tissues. They may be cultivated upon nutrient gelatin, blood-serum, and neutralized bouillon, as well as upon potatoes. They form white colonies. Feeding or inoculation of the bacilli causes in chickens a typical chicken-cholera; pigeons, sparrows, pheasants, rabbits, and mice are also susceptible to the bacilli. In sheep, horses, and guinea-pigs they produce abscesses at the point of inoculation.

Literature.

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Kitt: Geflügelcholera. Cbl. f. Bakt., i., 1887; Deut. Zeitschr. f. Thiermed., xiii., 1888.
Pasteur: Compt. rend., xc., 1880.
Wertheim: Cholera gallinarum. A. f. exp. Path., 26 Bd., 1889.
Zürn: Die Krankheiten des Hausgeflügels, Weimar, 1882.

The **Bacillus diphtheriae columbarum** is a small, slender bacillus, which was isolated by Löffler (" Mittheil. a. d. k. Ges.-Amte," ii.) from the exudate of a pigeon dying of diphtheria, and is regarded (*Babes* and *Puscarin*, " Unters. über die Diphtherie der Tauben," *Zeitschr. f. Hyg.*, viii., 1890) as the probable cause of pigeon-diphtheria, a disease resembling human diphtheria. Löffler was able to reproduce the disease in pigeons, but not in chickens, by means of inoculation of pure cultures of the bacilli. Mice died in about five days after inoculation, and the bacilli were found in the blood-vessels of all the organs. Streit (" Unters. über Geflügel-Diphtherie," *Z. f. Hyg.*, 46 Bd., 1904) found a bacillus in *chicken diphtheria* which he was able to cultivate and inoculate successfully in pigeons.

As the **Necrosis Bacillus** (*Bacillus necrophorus, Flügge; Bacillus necroseos, Salomonsen; Streptothrix necrophora, Kitt, Streptothrix caniculæ, Schmorl*) there has been described an anaërobic bacterium (*Jensen*: " Nekrose Bacillus." " Handb. d. pathog. Mikroorg.," ii., Jena, 1903) which forms rods and unbranched threads, does not stain according to Gram's method, and produces gas in cultures. It has been observed in all the domestic animals, including the chicken. It causes inflammations in the hoof of the horse, cattle, and reindeer, and on the tail, foot, and udder of swine and cows, and is the cause of the so-called *calves' diphtheria* (*Löffler*), *rabbit diphtheria*, and, perhaps, also in part of *avian diphtheria*. In hogs also it causes necrotic inflammation of the mouth and nose. It has been found also in inflammations of the colon in horses, and in the vagina and in the uterus of cows, and in the inflamed umbilical cord of calves. It can also produce metastases in the internal organs. It occurs in the regions named above, and also in other parts of the body, partly as a primary infection, and partly secondary to some other infection.

Besides the above, there are many other bacilli which have been described as the cause of disease in animals. Thus, for example, according to *Höflich* (" Die Pyelonephritis bacillosa des Rindes," *Monatsh. f. prakt. Thierheilk.*, ref. *Centralb. f. Bakt.*, x.) and *Enderlen* (" Primäre infectiöse Pyelonephritis beim Rinde," *Deutsch. Zeitschr. f. Thiermed.*, xvii., 1891, ref. *Cent. f. Bakt.*, x.), the frequently occurring *pyelonephritis* of cattle is caused by a *bacillus*. Likewise, according to *Nocard* (" Note sur la maladie des bœufs de la Guadeloupe connue sous le nom de Farcin," *Ann. de l'In. Past.*, ii., 1888) the *worm disease of the ox*, which was formerly of frequent occurrence in France; and according to *Oreste* and *Armanni* (" Studii e ricerche intorno al barbone dei bufali," ref. *Cent. f. Bakt.*, ii., 1887) and *von Ratz* (" Die Barbonekrankheit," *Deutsch. Zeitschr. f. Thiermed.*, xxii., 1896), the plague occurring among the Italian buffalo known as *barbone dei bufali* is due to a *bacillus* (by *Voges* regarded as the bacillus of hæmorrhagic septicæmia).

In the *dysentery of calves* different bacilli, including the bacterium coli, have been described as the cause (*Joest:* " Untersuchungen über Kälberruhr," *Z. f. Tiermed.*, vii., Jena, 1903; *Jensen:* "Handb. d. path. Mikroorg.," iii., Jena, 1903). According to

Nocard and *Roux* ("Le microbe de la péripneumonie," *Ann. de l'Inst. Pasteur*, 1898), the *lung plague* of *cattle* is characterized by a very small, lively motile bacillus whose form is determined with difficulty. According to *Bang* ("Aetiologie des seuchenhaften Verwerfens," *Zeitschr. f. Tiermed.*, i., 1887) and *Preisz* ("Bacillus des seuchenhaften Verwerfens," *C. f. B., Orig.*, xxxiii., 1903) bacilli cause the epidemic abortion of cattle.

Lundgren ("Die Renntierpest," *Zeitschr. f. Tiermed.*, ii., 1898) and *Bergman* ("Renntierpest und Renntierpestbacillen," *ib.*, v., 1901) on the ground of their investigations regard certain bacilli as causing reindeer plague. The contagium of reindeer pest is yet unknown (*Kolle:* "Rinderpest," *Ergebn. d. allg. Path.*, vi., Wiesbaden, 1901). Likewise the cause of the hoof-and-mouth disease is still unknown (*Löffler:* "Bericht über d. Untersuch. d. ii. preuss. Kommission," *D. med. Woch.*, 1903). It passes through all filters.

3. The Spirilla and the Diseases Caused by Them.

(a) *General Remarks upon the Spirilla.*

§ 178. The **Spirilla**, or **Spirillaceæ**, or **Spirobacteria** are divided into two genera, one of them called *Spirillum*, the other *Spirochæte*. Many writers recognize still another genus, *Vibrio*.

The genus **Spirillum** is characterized by the formation of short, stiff, shallow spirals, which in part possess flagella and show an active swarming movement. The wavy rods are also called **vibriones** by many writers.

The genus **Spirochæte** is characterized by long, flexible, closely turned spirals.

The *Spirochæte plicatilis* forms long, very fine, closely wound threads, from 100–225 μ long; it is of frequent occurrence in swamp-water and in gutters, and makes very rapid movements.

Spirochæte buccalis sive **denticola** is 10–20 μ long, pointed at both ends, and is not infrequently observed in the secretions of the mouth and nose (cf. Fig. 196). It appears to possess no pathogenic significance.

Spirillum sive *Vibrio rugula* (Fig. 512, *b*) forms rods, from 6–16 μ long and 0.5–2.5 μ broad, simply bent or having a shallow turn, and moves by means of flagella. It occurs in swamp-water, fæces, and in the slime from the teeth.

Spirillum sive *Vibrio serpens* forms thin threads from 11–28 μ long, having three to four wavy turns, and is found in stagnating fluids.

Spirillum tenue has very thin threads about 3–15 μ long, having 2–5 screw-like turns.

Spirillum undula (Fig. 512, *a*) consists of a thread from 1–1.5 μ broad and 8–12 μ long, having from one and a half to three turns, and furnished with a flagellum at one end. It occurs in various decomposing fluids and executes rapid twisting and darting movements.

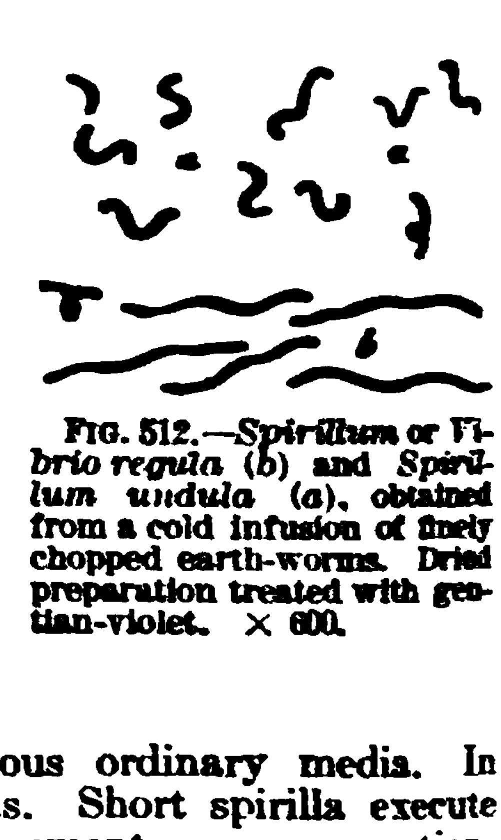

FIG. 512.—*Spirillum* or *Vibrio rugula* (*b*) and *Spirillum undula* (*a*), obtained from a cold infusion of finely chopped earth-worms. Dried preparation treated with gentian-violet. × 600.

Spirillum volutans possesses threads 1.5–2 μ thick and 25–30 μ long, with two and a half to three and a half turns, and bearing a flagellum at each end.

According to *Prazmowski*, *Spirillum rugula* causes decomposition of cellulose, and forms terminal spores. According to *Weibel*, a vibrio present in nasal slime presents many forms of growth. *Esmarch* succeeded in cultivating a spirillum, called by him *Spirillum rubrum*, upon the various ordinary media. In bouillon it forms spirals of from forty-three to fifty turns. Short spirilla execute lively movements, but long ones, on the contrary, slow movements, or are motionless. The colonies in firm nutrient media are at the beginning pale, but in time the portions not exposed to the air take on a wine-red color. In the spirilla of old cultures there appear three to four clear, dull-glistening spots that do not stain, and are probably to be regarded as spores. Cultures which contain such spirilla are more resistant to drying than others, but they are very easily killed by heat.

The long spirals may break up into short segments which possess only about three-quarters of a turn, but these may again grow in length, and undergo division. Branching has been observed many times (*Kutscher*, *Zettnow*, *Reichenbach*).

Literature.

(Life-history of the Spirilla.)

Esmarch: Ueber die Reinkultur eines Spirillum. Cbl. f. Bakt., i., 1887.
Kitasato: Reinkultur eines Spirillum aus faulendem Blute. Cbl. f. Bakt., iii., 1888.
Kutscher: Vibrionen u. Spirillenflora d. Düngerjauche. Zeitschr. f. Hyg., xx., 1895; Spirillum Undula minus u. majus. Cbl. f. Bakt., xviii., 1895.
Prazmowsky: Unters. üb. die Entwickelungsgeschichte einiger Bakterien, Leipzig, 1888.
Reichenbach: Ueber Verzweigungen bei Spirillen. Cbl. f. Bakt., xxix., 1901.
Salomon: Spirillum d. Säugethiermagens. Cbl. f. Bakt., xix., 1896.
Weibel: Untersuchungen über Vibrionen. Cbl. f. Bakt., ii., 1887, iv., 1888.
Zettnow: Bau der grossen Spirillen. Z. f. Hyg., xxiv., 1897.

(b) The Pathogenic Spirilla.

§ 179. The **Spirillum choleræ asiaticæ,** or the *Vibrio choleræ,* also called *comma-bacillus* (*bacille-virgule cholérigène*), was discovered by R. Koch in 1884, and is regarded as the cause of Asiatic cholera. The spirilla (Fig. 513) form small *comma-like, curved rods,* from 0.8–2 μ long.

Cultures of cholera-spirilla may be obtained upon a great variety of culture-media of a slightly alkaline reaction. The temperatures most favorable for their development lie between 25° and 30° C.; at between 16° and 8° C. they are still capable of a feeble development.

FIG. 513.—Cholera-spirilla from a pure culture. Cover-glass preparation stained with fuchsin. × 400.

In fluid media in the presence of oxygen they show lively movements that may be easily observed in the hanging drop. The movements are produced by means of a *terminal flagellum.*

When gaining entrance to the *intestinal tract of man* the spirilla, in so far as they are not destroyed by the action of the gastric juice or their growth otherwise prevented, develop both in the small and large intestines, and their multiplication is followed by a marked transudation from the intestinal mucosa, so that the intestine becomes filled with a fluid resembling meal-soup or rice-water, in which flakes of desquamated epithelium which has undergone mucoid degeneration float about.

The spirilla are always present in great numbers in the intestinal contents, and are found in the lumina of the intestinal glands, whence they may penetrate between and beneath the epithelial cells.

In recent cases the spirilla may usually be demonstrated in cover-glass preparations stained with methylene-blue or fuchsin. Fresh dejecta, as well as soiled linen, are suitable for the examination, since, according to observations made by Koch, the spirilla may multiply actively for some time upon moist linen and moist earth. In old cases the demonstration of the spirilla is more difficult, but nevertheless succeeds in all cases, and is attainable most surely by means of plate-cultures.

The *presence of cholera-spirilla in the intestine excites an inflammation,* which in the beginning finds expression in redness, swelling, marked transudation, mucoid degeneration of the epithelium, and desquamation; later, by hæmorrhages, formation of sloughs, and ulceration. It is characterized constantly by a more or less marked cellular infiltration of the

tissues. The solitary follicles and Peyer's patches are swollen even in fresh cases. Death may take place after a few hours or after one to three days. If the disease lasts a longer time, the intestinal contents become more consistent and the intestinal mucosa shows ulcerative changes.

According to our present knowledge, the spirilla produce poisonous substances which cause local damage to the mucosa of the intestinal canal, and when absorbed give rise to symptoms of intoxication and cause paralysis of the vessels. Small foci of degeneration are often present in the liver and kidneys, within which the gland-cells show cloudy, fatty, or hyaline degeneration, or are necrotic. Moreover, the kidneys may frequently show cloudiness caused by a toxic degeneration of the epithelium; occasionally also a swelling of the cortex. Ecchymoses in the epicardium are of frequent occurrence, and in the later stages patches of necrosis may also occur in the mucous membrane of the vagina. The long-continued presence of spirilla in the intestine may give rise to ulceration. Finally, the spirilla may be crowded out by the putrefactive bacteria present in the intestine, and ultimately die out. Through the absorption of the products of decomposition a new intoxication may arise, which is not dependent upon the original spirilla.

According to Koch, Nicati, and Rietsch, cholera-spirilla may also be found in the vomitus. Nicati, Rietsch, Tizzoni, and Cattani found them also in the ductus choledochus and in the gall-bladder. According to the statements of these authors the spirilla usually do not enter the blood, but in cases of severe infection they may be spread throughout the body.

Koch demonstrated the presence of spirilla in a tank in India which furnished the inhabitants of the region with their entire supply of water for drinking and other purposes, at a time when a part of the inhabitants were sick and dying of cholera. Since then, they have often been demonstrated in water-supplies during cholera epidemics.

Asiatic cholera is endemic in Lower Bengal and never entirely disappears there. Thence it spreads at times throughout India, and is carried by transportation over a larger or smaller part of the world. Since the spirilla are easily killed outside of the body the transportation must be effected mainly by individuals suffering from the disease. The infection probably occurs exclusively through the alimentary tract, as the result of the introduction of infected beverages, food, or some other substance into the mouth; but without doubt not every introduction of cholera-spirilla into the intestinal canal is followed by infection.

Moreover, it not infrequently happens that the spirilla increase in the intestine, but excite only slight changes, so that the infected individual suffers no marked symptoms, and the diagnosis can only be made through the demonstration of spirilla in the stools.

If the cholera-spirilla get into the water-supply and there increase, cholera may develop in the given region with very great rapidity. If, on the contrary, the infection takes place by direct or indirect contagion from man to man, the spread is slow, in that the disease is confined to those who come into contact with the sick, or with articles contaminated by the latter. The incubation period is from one to two days.

In the intestines of convalescents the spirilla, according to investigations of Kolle, may live for a long time and multiply without giving rise to any symptoms betraying their presence. Kolle was able to demon

strate them in a number of cases after five to eighteen days, and in individual cases as long as twenty to forty-eight days.

One attack of cholera makes the individual immune for a certain time. The immunity depends upon the presence of bactericidal anti bodies. Through these bodies the organism may be protected from cholera; but in those who have already contracted the disease the protective influence is of no avail (cf. § 32).

On gelatin-plates **cultures of cholera-spirilla** form round, flat, yellowish discs which liquefy the gelatin only slowly. At a low magnification the cultures are irregular in outline, and of a granular or furrowed and rough surface, appearing as if strewn with small particles of glass (*Koch*). Through the liquefaction of the gelatin in its immediate neighborhood there is formed a funnel-shaped cavity, to the bottom of which the colony sinks.

Stab-cultures in gelatin form on the second day a whitish cord corresponding to the line of the stab (Fig. 514), in the immediate neighborhood of which the gelatin is liquefied. The canal thus formed widens out above into a funnel part which is filled in its lower portion with liquefied gelatin and in its upper with air. The widening of the funnel of the canal of inoculation takes place very slowly, so that its edge reaches the wall of the tube only after five to six days.

On potatoes at from 30°–35° C. the spirilla form light-brown cultures, on agar-agar grayish-yellow slimy cultures. They grow also in bouillon, blood-serum, and milk.

They do not increase in pure water (*Bolton*), but do so in water contaminated with substances furnishing nutrient material.

The cholera-spirilla are aërobic, but they are also able to grow under anaërobic conditions. According to investigations by *Hueppe*, cultivation with a deficient supply of oxygen increases the virulence of the culture; but the resisting power against injurious agents—for example, against acids—is on the other hand lowered; with free access of oxygen the reverse takes place. *Pfeiffer*, however, found that young cultures grown in the presence of oxygen also contained poison. The spirilla present in fresh dejections (*Hueppe*) are easily killed, and have but little infecting power; whereas the growth of the spirilla outside of the body increases their resistance (for example, against the gastric juice) and makes them at the same time more capable of causing infection in new individuals. They are easily destroyed by desiccation in free air (*Guyon*) and by high temperatures, and by boiling for a short time. They are easily supplanted by saprophytic bacteria when the nutrient material and the temperature are not suitable. In the contents of privy-vaults they soon die out (*Koch*). They are very easily killed by acids, mercuric chloride, and carbolic acid. According to observations by *Koch*, they may live in well water for thirty days, in sewage for seven days, and on damp linen for three to four days. *Nicati* and *Reitsch* found them alive after eighty-one days in water taken from the harbor of Marseilles.

In cultures they sometimes form short rods, more or less curved (Fig. 513) and often joined in pairs, at other times they form long spirals. With these there also occur straight rods, and occasionally the majority form rods which show the curve only imperfectly or not at all.

At a certain degree of exhaustion of the food-material there frequently appear involution forms, in which the rods are sometimes shrunken, sometimes swollen, thus creating a great variety of forms. A globular swelling, as well as the formation of spots which do not take the stain in stained preparations, occurs as the result of degeneration, and have often been erroneously interpreted as phenomena of fructification. Spore formation has not been demonstrated. The addition of hydrochloric or sulphuric acid to cultures of cholera-spirilla in peptone-containing media (peptone-meat-infusion or an alkaline, one-per-cent solution of peptone containing one per cent of salt) causes the culture to assume a rose-red or Burgundy-red color, due to the

FIG. 514. Stab-culture, in gelatin, of cholera-spirilla.

formation of a coloring-matter, *cholera-red*. According to *Salkowski*, this is a nitroso-indol reaction.

In order to facilitate the separation of cholera-spirilla from other intestinal bacteria, *Schottelius* recommends the mixing of the dejecta with double the amount of a slightly alkaline meat-infusion, and allowing the mixture to remain uncovered for twelve hours at a temperature of from 30°–40° C. The spirilla requiring oxygen will develop particularly upon the surface, and may be easily transferred thence to plate-cultures. *Koch* recommends for this purpose a solution of peptone with common salt.

According to investigations by *Nicati*, *Rietsch*, *van Ermengem*, and *Koch*, symptoms resembling cholera may be produced in experimental animals through the introduction of cholera-spirilla into the intestinal canal. This experiment succeeds when cultures are introduced directly into the duodenum or small intestine (*Nicati* and *Rietsch*), as well as when the gastric juice of the animals (guinea-pigs) is neutralized with a five-per-cent. solution of soda, the bowels being quieted by an injection of 1 c.c. of tincture of opium to every 200 gm. of the body-weight, and one or more drops of a pure culture of the spirilla then introduced into the stomach (*Koch*).

The animals thus inoculated die with marked symptoms of collapse. The small intestine is found to be filled with a watery, flocculent, colorless fluid containing spirilla in great numbers; the intestinal mucosa is reddened and swollen.

The poison which is produced by the cholera-bacillus and which causes the essential clinical symptoms of a cholera-infection is not known. *Gamaleia* believes that it is a nucleo-albumin. *Scholl*, that it is a peptone (cholera-toxopeptone). *Pfeiffer* is of the opinion that it is an element of the cell-body. According to *Metschnikoff* and others, it is secreted by the cells. According to *Gamaleia*, it is probably an endotoxin which is very labile and easily passes over to a secondary poisonous mixture rich in toxoids. [illegible] the spirilla contain a bacterial protein which is not specific and which excites inflammation.

The virulence of cholera-cultures differs greatly according to the place of origin and the age. The virulence decreases with the age. Guinea-pigs which are very susceptible to intraperitoneal inoculations of cholera may be protected against this infection by the intraperitoneal injection of attenuated cultures, but no absolute immunity can be produced in this way. The blood-serum of human individuals that have recovered from an attack of cholera shows protective properties for guinea-pigs for several weeks after the attack.

The nitroso-indol reaction in cultures of the cholera-spirillum is due to the fact that the cholera-spirillum in peptone solutions not only forms indol but also nitrites. The addition of hydrochloric or sulphuric acid sets free nitrous acid which forms a red color with indol. With the *Spirillum of Finkler*, the *Spirillum of Metschnikoff*, and the *Spirillum of Deneke*, which also produce indol, the red color of the cultures occurs only when potassium nitrite is added with sulphuric acid, or when nitrous acid alone is added.

Spirilla Resembling the Cholera-Spirillum.

[illegible] The *Spirillum of Finkler and Prior*, found by these observers in the dejecta of persons suffering from cholera nostras, after the discharges have stood for some time in a vessel. The spirilla are very similar to the cholera-spirilla, but somewhat larger and thicker. In plate-cultures they are distinguished from the latter only in the fact that the small colonies are not distinctly granular and have a sharp contour. Gelatin is [illegible] and subsequently in stab-cultures after twenty-four hours a [illegible] with [illegible] fluid [illegible] is formed, which soon reaches the walls of the tube.

[illegible] temperatures, they form within forty-eight hours a [illegible] marked off from the substance of the potato [illegible] the cholera-spirilla do not grow at all at room-temperature, and [illegible].

[illegible] and are rather resistant to drying. [illegible] guinea-pigs [illegible] the medical [illegible] similar to those [illegible] cholera-spirilla, but less intense.

[illegible] *Finkler and Prior* possesses a [illegible] from which these investigators [illegible] to find the spirilla [illegible] "cholera nostras." *Knisl* [illegible] 1885, on the other hand, [illegible]

(2) *Spirillum tyrogenum*, found in cheese by *Deneke* in Flügge's Institute (*Deut. med. Wochenschr.*, 1885), is also very much like the cholera-spirillum, but is somewhat smaller, and the long spiral threads are more closely wound. Cultures on gelatin-plates form at first sharply contoured discs that by low magnification appear dark, and liquefy the gelatin more rapidly than the spirillum of Koch. In stab-cultures they behave like the Finkler-Prior spirillum, but do not grow upon potato.

(3) *Spirillum sputigenum* is a spirillum of the shape of a curved rod, somewhat longer and thinner than the cholera-spirillum. It occurs in the saliva, and cannot be cultivated upon the ordinary media.

(4) *Vibrio of Metschnikoff* (*Gamaleia*, "Vibrio Metschnikovi et ses rapports avec le microbe du cholera asiatique," *Annal. d. l'Inst. Past.*, ii., 1888; iii., 1889; *Pfeiffer*, "Ueber den Vibrio Metschnikovi und sein Verhältniss zur Cholera asiatica," *Zeitschr. f. Hyg.*, 1889) is a fission fungus isolated by Gamaleïa in an epidemic occurring in chickens in Odessa, which was characterized by diarrhœa and enteritis. When cultivated it shows a very great resemblance to the cholera-spirillum of Koch. The spirillum is most easily obtained pure by inoculating pigeons with the blood of diseased chickens. The pigeons die in from twelve to twenty hours and show the spirilla in the blood and in the intestinal tract.

Ziegler has transferred **Relapsing Fever** to the protozoan diseases, following *Schaudinn's* view that the spirochætes are protozoa. If this opinion be correct, **Syphilis** should likewise be classed with the protozoan infections. As mentioned below, the correctness of such a view is doubted by other writers (*Novy*), who believe that the spirochætes are bacterial and are to be classed with the spirilla.

FIG. 515. Stab-culture, in gelatin, of the *Spirillum of Finkler* and *Prior*.

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CHAPTER XI.

The Yeasts and Moulds, and the Diseases Caused by Them.

§ 180. The **yeasts (Blastomycetes)** and the **moulds (Hyphomycetes)** belong, as do the schizomycetes, to the non-chlorophyllaceous thallophytes. With the schizomycetes they have no phylogenetic relationship; on the other hand, they are closely related to one another, and both belong to the branching fungi or the eumycetes.

The moulds and yeasts, like the schizomycetes, derive their nourishment from organic substances containing carbon. The majority find their food in dead organic substances, and belong therefore to the *saprophytes;* some are able to obtain nourishment from living tissues, and are to be classed, at least at times, with the *parasites.* In human beings both forms occur.

Outside the organism the moulds are generally known as the producers of the different mouldy films which so frequently develop upon organic substances. They belong to different groups of fungi.

The yeast-fungi are the cause of alcoholic fermentation, and form the scum on the top of alcoholic beverages.

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§ 181. **Yeasts** occur in man in the form of *naked* or *encapsulated, oval* or *round cells* of varying size. They are found chiefly as harmless **saprophytes,** most frequently in the upper part of the intestinal canal—in the stomach—where they are almost constantly present; and when beverages in the process of alcoholic fermentation are taken they may occur in large numbers, and may also multiply. In the bladder they may likewise multiply, in case the urine contains sugar; and may cause fermentation of the urine with evolution of carbonic-acid gas.

As **parasites** no importance has been attached to them until very recently, but the investigations of Busse, Buschke, Sanfelice, Curtis, and

others have established the fact that there are also *species of Saccharomycetes of pathogenic importance.* According to these observations the pathogenic yeasts can multiply in different tissues, in the skin, periosteum, lungs, and glandular organs, and can excite either *purulent inflammations*, or *proliferations of granulation tissue*, which run a course similar to that of an infection with actinomycosis or tuberculosis. In inflammatory foci the yeast cells are for the chief part provided with a capsule. They may be present in large numbers so that through their mass alone they may give rise to tumor-like swellings. Through degenerative changes, crescentic forms may develop from the oval yeast-cells.

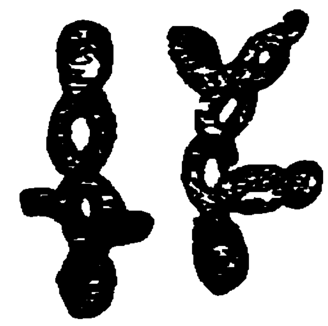

Fig. 516.—*Saccharomyces ellipsoideus.* × [illegible].

In solutions containing sugar the blastomycetes form oval cells (Fig. 516). Reproduction takes place through budding and constriction; on any portion of the parent cell there may develop an excrescence, which is constricted off after it reaches the size of the mother cell. Under certain conditions the cells may grow out into threads or hyphæ, but in these threads no subsequent segmentation occur; jointed threads arise through budding. A dilute culture-medium favors the formation of threads.

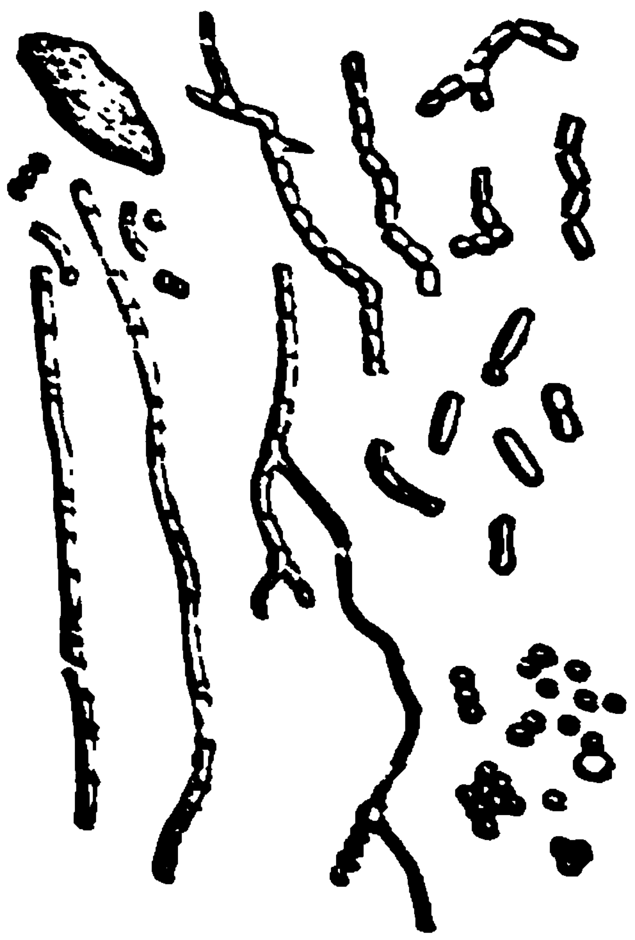

Fig. 517.—Fresh favus-mass consisting of hyphæ, conidia, and epithelial cells. (After Neumann.)

Mould-fungi are found in man partly in the form of simple or branched, unjointed or jointed threads of varying thickness; and partly as oblong or even as spherical cells. The threads are designated as **hyphæ** (Figs. 517, 518), and the mass which they form as **mycelium**; the spherical or long oval or short cylindrical cells, which are frequently arranged in the form of a rosary, as **spores**, or better as **conidia-spores** (Figs. 517, 518). Only rarely has there been observed within the body a fructification upon special fruit-organs.

The moulds are partly **saprophytes** and partly **parasites**; and are found almost exclusively in regions accessible from without, as the skin, intestinal canal, respiratory tract, external ear, vagina, etc. Only exceptionally, and under especial conditions, do they reach the internal organs, as, for example, the brain. It is evident that, on the whole, the living tissues of the human organism do not afford a suitable nutrient medium for the mould-fungi, and the life-activities of the tissue-cells for the greater part do not permit their development and multiplication. The need for oxygen prevents the growth of moulds in many tissues; and for many moulds the temperature of the body is too high. Moreover, the chemical composition of the tissues does not offer to the moulds a favorable mixture of nutrient material.

Fig. 518.—From a growth of [illegible] on the tongue of a man dying of [illegible] pneumonia fever. [illegible]

Moulds growing as saprophytes occur in man most frequently in the alimentary canal, particularly in the *mouth, pharynx,* and *œsophagus.* They develop in these regions particularly when the ingesta or desquamated cells lie undisturbed in one position for a long time, and when the function of the organ concerned is lowered. They are recognized through the formation of hyphæ and conidia.

In the external *auditory canal* moulds grow especially in abnormal masses which fill up the passage and consist in part of cerumen, or of inflammatory exudates and desquamated cells, and in part of substances introduced from without.

In the *lungs* moulds are occasionally found upon the necrotic wall of cavities, particularly those due to tuberculosis, as well as in necrotic and gangrenous hæmorrhagic infarcts, etc. In the air-passages they are observed most frequently in bronchiectases.

In the alimentary tract, as well as in the ear and lungs, the moulds form chiefly a whitish deposit on or in the tissues. In the event of fructification upon especial fruit-bearers they may take on a brown, gray, or even black appearance. In the intestinal canal the food and drink may give them various colors.

At first the moulds grow in dead material, but they may penetrate thence more or less extensively into living tissue; and cases have been observed in which they have even entered the circulation and have been

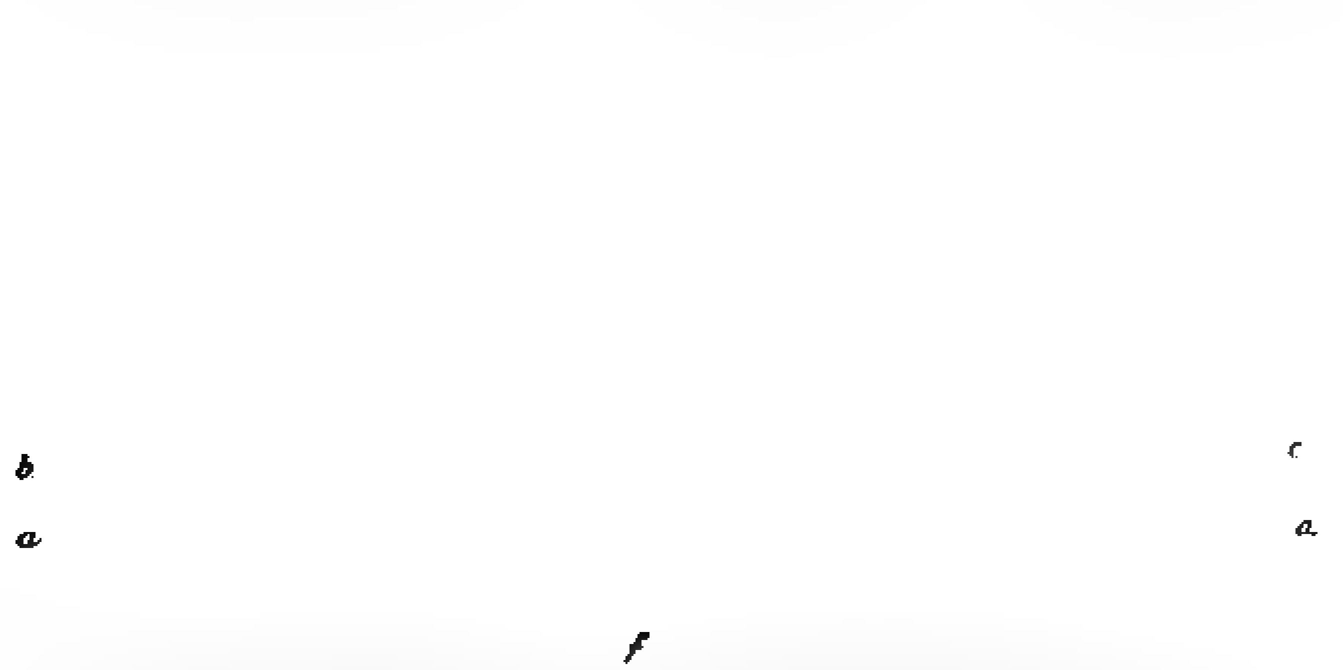

FIG. 519.—Section through a thrush-covered œsophagus of a small child (alcohol, carmine, Gram's). *a*, Connective tissue; *b*, normal epithelium; *c*, swollen and desquamated epithelium infiltrated with fungus-threads; *d*, epithelium infiltrated with cells; *e*, cocci and bacilli; *f*, cellular focus in the connective tissue. × 25.

carried by the blood-stream to distant organs. Thus the fungous growth called **thrush** which appears chiefly upon the mucous membrane of the *mouth, pharynx,* and *œsophagus,* and more rarely upon that of the *stomach, intestine,* and *vagina,* and upon the *nipples* of nursing women, cannot be regarded as a pure saprophytic, but, on the contrary, is a **parasitic growth,** which penetrates into living epithelium (Fig. 519, *c*), and even into the underlying connective tissue. It is true, however, that thrush occurs chiefly in infants and in debilitated invalids who are no longer able to cleanse the mouth, throat, and œsophagus, so that some especial local predisposition appears to be necessary for its development, and it is probable that the primary colonization of the fungus takes place in dead material. Nevertheless, there occurs then an active penetration

into living tissue—that is, first into the epithelium (*c*, *d*), but often also into the connective tissue (*a*, *f*), and into the blood-vessels, and from these portals of invasion there may develop metastases in the internal organs. Thus, Zenker has observed hyphæ and conidia in an abscess of the brain; and Paltauf has reported a case in which a mould-fungus was conveyed from an intestinal ulcer to the brain and lung. Schmorl and Heubner have described thrush-metastases in the kidneys.

Moreover, **growths of moulds in the lungs** are not always confined to dead material or to the cavity of the bronchus, but it happens, though rarely, that they penetrate into the living respiratory parenchyma, forming small white or yellowish, nodular masses, within which the lung tissue is necrotic, while in the neighborhood there is formed an inflammatory infiltration. In the injured *cornea* they may likewise penetrate into the tissue and cause necrosis and inflammation.

Local **colonizations of moulds which penetrate into living tissue** cause a more or less marked irritation of the surrounding tissues, and give rise to *tissue-degenerations* (Fig. 519, *c*) and *inflammation*. Such changes may be observed in mycosis of the lung, as well as of the intestine (*c*, *d*, *f*) and ear. When invading the lungs they form growths of hyphæ which resemble the granules of actinomycosis, and are surrounded by collections of cells. Their action, however, is always limited, and they produce no substances which are injurious to the organism as a whole, or cause symptoms of poisoning. The frequently reported finding of moulds in abscesses of the subcutaneous tissues and internal organs are probably to be interpreted as due to the fact, that along with the bacteria causing the suppuration, moulds also get into the tissues, as well as into the circulation. A general spreading of mould-fungi does not occur in these cases, in that the further development of the same is confined to the place of the metastasis.

The moulds which are saprophytic, or are to a limited extent parasitic in man, belong to the **Mucor, Aspergillus,** and **Eurotium** genera. From the ear various species have been obtained: *Aspergillus fumigatus* (Fresen), *Aspergillus flavus* or *flavescens* (Brefeld, Wreden), *Aspergillus niger* or *nigricans* (Van Tieghem, Wreden, Wilhelm), *Aspergillus nidulans* (Eidam), *Eurotium malignum* (Lindt), *Mucor corymbifer*, and *Trichothecium roseum;* and, in so far as known, these are the same species which occasionally occur in the respiratory tract.

In the majority of cases it is necessary, in order to determine the variety of mould, to make cultures upon suitable nutrient media (decoction of bread, bread-agar, potato, gelatin, etc.). On these the conidia which are sown grow out into germ-tubes, and form simple or branched, unicellular or multicellular threads, on which arise the peculiarly constructed fruit-bearers characteristic of the species, which eventually produce conidia. Many also form spores through the copulation of cells of the mycelia, especially when the supply of oxygen is lowered (Brefeld, Siebenmann).

In the mucors there appear especial *fruit-bearers* (Fig. 520, *c*), which according to the species are either single or branched, and on the ends of which there are knob-like swellings from which the *sporangia* (*d*)—that is, spherical vesicles filled with conidia-spores—grow.

Mucor corymbifer, for example, forms branched fruit-bearers (Fig. 520, *c*). The sporangia (*d*) on the ends possess a smooth membrane and enclose at the time of ripening yellowish conidia-spores.

The aspergilli form *conidia-bearers*, which swell out spherically above, and then produce numerous *sterigmata*—that is, cone-like outgrowths, radially arranged, thickly crowded, and sprouting out from the upper half of the sphere. From each sterigma a *chain of conidia* is later constricted off (Fig. 521, *a*, *b*).

FIG. 520.—*Mucor corymbifer* in fructification (culture upon glass-slide). *a*, Aerial hyphæ; *b*, mycelia lying within the nutrient gelatin; *c*, branching fruit-bearers; *d*, sporangia. × 100.

The *botanical position of the fungus of thrush* is still unsettled. Formerly it was called **Oidium albicans**, and classed with the genus Oïdium, which occurs in different species in the form of filmy coatings upon organic substances. When cultivated from conidia it produces hyphæ which become jointed and develop conidia through a transverse division of the threads, but form no peculiar fruit-bearers.

According to Rees, Grawitz, Kehrer, the thrush-fungus grows by budding and by the production of mycelia and conidia, which in turn produce at their ends, by a process of constriction, new conidia, in a manner similar to that which takes place in the forms of mycoderma belonging to the yeast-fungi. Consequently this fungus should be designated *Mycoderma albicans*. Linossier and Roux are, however, of the opinion that the thrush-fungus does not belong at all to the saccharomycetes, and they regard its classification at the present time as impossible. Caō, who has investigated numerous *varieties of oïdium*, regards the oïdia as a well-defined class of fungi standing between the blastomycetes and the hyphomycetes, which they approach through their production of mycelia.

FIG. 521.—Hyphæ with conidia-bearers of *Aspergillus fumigatus*. *a*, Fruit-head in optical cross-section; *b*, fruit-head seen from above. × 275.

According to Plaut the thrush-fungus is identical with a mould, *Monilia candida*, which occurs frequently in nature. Kehrer suspects that it is one of the higher moulds which has become degenerated through parasitism.

According to *Neumayer* all *varieties of yeasts* are resistant to the digestive juices, and may pass through the human intestinal tract without being killed. Without the coincident introduction of some fermentable substance they are harmless. They exert an influence upon the intestinal canal only when fermentable substances are introduced, whereby at the high temperature of the body abnormal products of fermentation are produced having an irritating action upon the intestinal tract.

Busse found (1894) great numbers of yeast-cells developing in the diseased areas present in a woman, thirty-one years of age, who died from multiple inflammations of the bones, skin, lungs, kidneys, and spleen, partly tumor-like and partly abscess-forming. According to his findings it may be regarded as certain that the yeast was the cause of the disease. The yeast could be easily cultivated upon suitable media. Mice were particularly susceptible to inoculation, dying in from four to eighty-three days after the injection. At death the yeast-cells were found to have markedly increased both at the point of inoculation, and also in the internal organs. A proliferation of tissue occurred only after a long duration of the infection.

Buschke found yeasts in multiple ulcers of head and neck, arising from acne-like lesions. *Gilchrist* and *Stokes* found yeasts in a lupus-like affection of the skin. *Loewenbach* and *Oppenheim* found a yeast in the skin of the nose showing formation of nodules and scar-tissue.

In 1896 *Gilchrist* reported observations on a peculiar progressive affection of the skin characterized by epithelial hyperplasia, miliary abscesses, and infiltration of the cutis. In the abscesses doubly-contoured refractive, round and oval bodies were found. They varied in size from 10–20 μ and presented buds of varying size. To this organism the name of *Blastomyces dermatitidis* was given, and the skin condition was called *blastomycetic dermatitis*. About fifty cases of this kind have since been reported, the majority of them by Chicago observers. In some of the cases a fatal generalized infection has been seen. The organisms cultivated from the cases fall into three groups: 1, a blastomycetoid; 2, an oidium-like; and 3, a hyphomycetoid group. According to *Ricketts* they may be included in a common genus, *Oidium*, and he has proposed the term *oidiomycosis* for the various lesions produced by these organisms. At the present time the exact botanical classification of the latter is not possible.

Under the designation of *coccidioidal granuloma* there have been reported eighteen cases (fourteen of these known to have lived in California) of a condition closely resembling oidiomycosis, but apparently differing from it in certain clinical characteristics and in the nature of the organisms found in the lesions. It runs a more severe and progressive course than the latter condition, and generalized infection is the rule. The organism multiplies by endogenous sporulation instead of by budding. *Ophüls* would class it with the oidia under the name of *Oidium coccidioides*. The lesions produced by it resemble tubercles closely in the majority of cases, and clinically the disease has been mistaken for tuberculosis.

Sanfelice experimented with yeasts from fruit-juices, and found among these one pathogenic for guinea-pigs (*Saccharomyces neoformans*) and one pathogenic for chickens and dogs (*Saccharomyces lithogenes*). *Curtis* found, in multiple proliferations of the skin resembling myxosarcoma, yeast-cells which were pathogenic for mice, rats, and dogs. *Cohn*, who experimented with the yeast described by *Klein*, found that its inoculation into the peritoneal cavity of mice caused death through the formation of great yeast-tumors. The intravenous injection of larger animals led to severe [illegible] of brain and spinal cord associated with inflammation of the [illegible] membranes, particularly of the [illegible].

Sanfelice, *Corselli*, *Frisco*, *Roncali*, *Binaghi*, *Leopold*, and others believe that blastomycetes may be the cause of true tumors, sarcoma and carcinoma. But true tumors have never yet been produced experimentally by inoculations of yeast-cells or by injection [illegible]. Only suppurations and inflammatory tissue-proliferations have been produced by such experiments, and the finding of yeast-like structures in true tumors, even if [illegible] these were true yeast-cells, does not permit of the conclusion that tumors are caused by yeasts.

According to the investigations of [illegible], [illegible], and [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] temperature, and, when introduced into the blood-current of animals, grow [illegible] [illegible] [illegible] although there [illegible] formation of mycelium, and apparently [illegible] [illegible] [illegible] beyond the area within which [illegible] have been introduced. [illegible] [illegible] [illegible] [illegible] [illegible] when introduced into the blood-stream of rabbits, chiefly in the kidneys and the [illegible] [illegible] in the intestines, where they cause a hemorrhagic inflammation. [illegible] [illegible] [illegible] [illegible] which, when injected into rabbits [illegible] abscesses [illegible] of granulation tissue, and many [illegible] [illegible] upon the organism.

According to [illegible] [illegible] which grows at summer temperature [illegible] [illegible] [illegible] [illegible] with [illegible] and [illegible] [illegible] [illegible] [illegible] growing [illegible] [illegible] [illegible].

[illegible] [illegible] of the [illegible] [illegible] are [illegible] in animals, [illegible]

cially in birds, and the proliferating mycelia cause tissue-necrosis and inflammation. According to *Chantemesse, Aspergillus fumigatus* causes in pigeons diseased conditions of the mouth, lungs, liver, and kidney, that of the first two organs resembling diphtheria, that of the latter two closely resembling tuberculosis. It may, therefore, be designated *pseudotuberculosis aspergillina.* According to *Potain*, the infection may be transmitted to man and give rise to ulcerative diseases of the lung.

Eurotium and *Aspergillus*, according to *Siebenmann*, are two different families, having, however, a close resemblance to each other, in that the mycelia and conidia are similarly formed. The essential differences between the two lie in the fact that *Eurotium* produces perithecia in the form of shining, light-yellow or sulphur-yellow. translucent bodies the size of a grain of sand, delicate and easily crushed, and which ultimately develop into spores capable of germination; while the true *Aspergillus* forms hard, woody sclerotia usually embedded in a thick, white matted mass of mycelia. The development of these takes place in two periods. The second part of the development occurs only when the sclerotium finds a lodgment upon a moist substratum.

Aspergillus flavus of *Brefeld* (*Eurotium Aspergillus flavus* of *de Bary*) forms golden yellow, green, and brown growths; round, yellow, olive-green, or brown fruit-heads; round, rarely oval, sulphur-yellow to brown conidia with minute warts on the surface; diameter 5–7 μ. *Aspergillus fumigatus* of *Fresen* (*Aspergillus nigrescens* of *Robin*) forms green, bluish, or gray growths; the fruit-heads are long, in shape resembling an inverted cone; conidia, round, rarely oval, smooth, mostly clear and colorless; diameter 2.5–3 μ. *Aspergillus niger* of *Van Tieghem* (*Eurotium Aspergillus niger* of *de Bary*) forms dark chocolate-brown growths; conidia are round, brownish-black, or grayish-brown when ripe; surface smooth or warty; diameter 3.6–5 μ.

Aspergillus can develop upon the injured cornea and give rise to purulent inflammation. *Leber* (*Graefe's Arch.*, xxv.) cultivated it upon the cornea and in the anterior chamber of the eye of the rabbit. Finally, *Aspergillus* also appears in the pelves of the kidneys. *Babes* (*Biol. Centralbl.*, ii.) found the conidia and hyphæ of a mould in ulcers of the skin which were covered by scabs, and gave to it the name of *Oidium subtile cutis.*

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§ 182. **Thread-fungi** are to be regarded as the **exciting cause of disease** in certain **affections of the skin,** as *favus, herpes tonsurans, pityriasis versicolor, erythrasma.* In all of these diseases the epithelial parts of the skin contain colonies of hyphæ and conidia, and there remains no doubt that their presence causes in part tissue-degenerations, and in part proliferations and inflammations.

The **fungus of favus** (Fig. 517) is usually called **Achorion Schönleini** (discovered by Schönlein in 1839).

Favus (*tinea favosa, scald-head*) affects particularly the hairy portions of the head, more rarely other regions, as, for example, the substance of the nails. It is characterized by the formation of discs (*favus scutula*), varying in size from that of a lentil to that of a five-cent piece, of a sulphur-yellow color, and indented or pierced by a hair. In an abortive course it may merely form scales similar to those of herpes.

According to Kaposi, the favus scutulum originates as a small, punctiform, yellow focus lying under the epidermis and penetrated by a hair. This grows in a few weeks to the size of a lentil and then forms a sulphur-yellow, indented disc showing through the upper layers of the skin. The scutulum consists of hyphæ and conidia spores, and lies in a cup-shaped depression of the skin, beneath the horny layer which is drawn away above it. If the mass be removed during life, the cavity shows a red moist surface. The favus itself forms a white, crumbling mass which is easily disintegrated in water.

If the scutula are not removed, they join together to form larger masses. When the epidermis is desquamated the favus-mass becomes exposed and dries up into a yellowish-white, mortar-like material. The hairs appear lustreless, as if covered with dust, and are easily pulled out, since the mycelia and conidia of the fungus penetrate into the hair-shaft and hair-bulb, as well as into the sheath of the hair-root.

Through the growth of the fungus-masses the hairs may not only be shed, but the papillæ may become atrophic. At the same time there is produced in the neighborhood of the hair-follicle a more or less intense inflammation which may take on an eczematous character.

The development of achorion in the nails (*onychomycosis favosa*) gives rise to sulphur-yellow deposits or uniform thickenings of the parenchyma of the nails with simultaneous loosening and cheesy disintegration of the same.

Trichophyton tonsurans, the fungus of **herpes tonsurans** (*"barber's*

itch," "*ringworm*"), consists of long narrow threads, branching but little, and with few conidia. It forms no sentulous masses, but penetrates easily into the hair-shaft, and makes the hairs brittle. It shows certain differences of growth, according to whether the herpes develops upon hairy surfaces or upon areas devoid of hairs.

Herpes or *Trichophytosis tonsurans capillitii* forms bare discs varying in size from that of a five-cent piece to that of a dollar. These spots in which the hairs are broken off short look like places in which the hair has been badly shaven. The surface is smooth or covered with scales, and somewhat reddened at the border of the disc. If the fungus-threads penetrate into the hair-follicles, pustules and scabs are formed. Such discs may appear in many places, and may constantly increase in size until healing finally takes place.

On places devoid of hairs the herpes forms vesicles (*Herpes tonsurans vesiculosus*), and red scaly spots, discs, and circles (*Herpes tonsurans squamosus*). At times red spots appear in numerous places; these quickly spread, and as rapidly heal. The fungus is found between the uppermost layers of the epidermis, just beneath the stratum corneum (Kaposi).

If trichophyton develops in the nail, the nail becomes cloudy, scales off, and is easily broken—a condition designated as *onychomycosis trichophytina*.

Sycosis parasitaria arises through the fact that the development of the fungus is accompanied by a severe inflammation of the hairy parts of the skin, leading to infiltration and suppuration—that is, to the formation of pustules, abscesses, and papillary proliferations. According to Kaposi and others **eczema marginatum** is also caused by the trichophyton tonsurans. The condition occurs in those regions where two surfaces of skin come into contact with each other and are macerated by sweat; and is characterized by the formation of vesicles, pustules, and scabs, which are situated in the periphery of a pigmented surface.

Microsporon furfur, the fungus of **pityriasis** or **mycosis versicolor** or **dermatomycosis furfuracea**, occurs likewise in the form of hyphæ and conidia, which are somewhat smaller than those of other skin-fungi. The pathological changes produced by this fungus are characterized by the formation of pale yellow or yellowish-brown to dark-brown and brownish-red spots, varying in size from that of a lentil to that of the hand, sometimes smooth and shining, at other times dull and exfoliating, and of irregular shape. They may be spread uniformly over large areas of skin; and are found chiefly upon the trunk, neck, and flexor surfaces of the extremities, but never upon the hands, feet, or face.

Microsporon minutissimum is the name given to a thread-fungus which is found in the skin affection known as **erythrasma** (von Bärensprung). The disease is characterized by the formation, on the inner side of the thigh, of brown or reddish-brown patches, which are only slightly scaly, and may be as large as the palm of the hand. The fungus is found in the epidermis, and is smaller than that of pityriasis.

The thread-fungi occurring in the diseased areas of the skin may be cultivated upon proper media (agar-agar, agar-glycerin, gelatin, potatoes, blood-serum, etc.), and on such the conidia develop into single and branching threads, which become jointed (Fig. 522, *a*), and form chains of short cells (*b*). Club-like formations which frequently appear upon the ends of the threads in cultures, are regarded by Quincke and Elsenberg as imperfect sporangia. The botanical position of these fungi is not yet determined; and nothing is known with

certainty concerning their distribution outside of the human and animal body.

According to *Quincke*, three forms of fungi occur in favus-masses, two of these being varieties of one species of fungus. *Elsenberg* found only two, which he regards as being varieties of the same species. *Pick, Plaut*, and *Biro* believe firmly in the etiological unity of favus.

Sabouraud advances the view that the fungi causing trichophytosis represent very different species, all of which belong to the genus *Botrytis*. *Krösing* distinguishes three groups of trichophyton-fungi according to the different appearances of the cultures on potato, and emphasizes, moreover, the differences in their organs of generation and fructification. *Rosenbach*, who has studied the moulds occurring in deep suppurating inflammations of the skin, differentiates several trichophyton-fungi as the cause of these affections.

According to *Spietschka*, the *Microsporon furfur* may be cultivated from the scales of the skin, and in cultures can be very well differentiated from the other pathogenic thread-fungi. Through the inoculation of the fungus a typical mycosis may be produced in man.

From the great number of recent investigations by various writers it is impossible to deduce anything definite concerning the number of kinds of favus- and trichophyton-fungi. It is, however, evident from these investigations that the nature of the nutrient medium is of great influence on the character of the growth (*Sabouraud, Waelsch*), and the difference in findings is to be referred in a great measure to differences in the nutrient media on which the moulds were grown.

FIG. 522. Culture of *Trichophyton tonsurans*. *a*, Branching threads with long joints which have delicate walls; *b*, threads with thick-walled, short segments, some of them being spherical. × 270.

Inoculations with fungi grown in cultures, into the skin of human beings, rabbits, mice, etc., which were made by *Grawitz, Boer, Münnich*, and others, gave partly negative, partly positive results. According to *Plaut*, the inoculations never give positive results when spore-formation has already taken place in the cultures.

Von Hebra has described (*Wiener med. Blätter*, 1881: "Die krankh. Veränd. d. Haut," Braunschweig, 1881) as *dermatomycosis diffusa flexorum* a peculiar itching dermatosis, which occurs on the elbow and bend of the knee and is thought to be caused by fungi, which are like those of *pityriasis versicolor*.

According to the investigations by *Wehmer*, the cause of the skin eruption known as *tokelau* which occurs in various South Sea Islands (Fiji, Samoa, and Solomon) and which is characterized by the formation of scaly rings, is an Aspergillus.

Favus and *herpes tonsurans* occur also in **domestic animals**, as well as in *mice* and *rats* (cf. *Friedeberger* and *Fröhner*, "Lehr. d. spec. Pathologie der Hausthiere"). *Waelsch* inoculated human individuals with favus fungi, which he had cultivated from mice affected with favus, and obtained typical favus scutularis.

Intravenous injections of favus-fungi into rabbits (*Bukovsky*) produced in the lungs of these animals a form of pseudotuberculosis; and cellular nodules are found in which fungus threads have developed in a manner suggesting the lesions of actinomycosis. After a time the fungi die.

In **invertebrate animals** there not infrequently occur diseases produced by mycelium-fungi. Thus *Botrytis Bassiani* causes the so-called *muscardine* in silkworms; *Cordyceps militaris* destroys the injurious pine-spider *Gastropachia pini*; *Tarichium megaspermum*, a black-colored fungus, kills the destructive earth-caterpillar *Agrotis segetum*. Fungi belonging to the genus *Empusa* attack especially the caterpillars of the cabbage-butterfly (*Empusa radicans*), and the house-fly (*Empusa muscæ*), their mycelia growing all through the caterpillar and finally killing it. *Achyla prolifera*, according to *Harz* (*Jahresber. d. Münchener Thierarzneischule*, 1882–83), grows through the musculature of crayfish, and is the cause of the crayfish-pest.

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CHAPTER XII.

The Animal Parasites and the Diseases Produced by Them.

I. Protozoa.

§ 183. Of the **Protozoa** occurring as parasites in man, only a small number was known up to a few years ago; and even the known forms possessed but slight significance, since there could be ascribed to them no marked influence upon the tissues. Through the investigations of the last few years, however, different forms have been recognized as the cause of morbid processes; and it is quite possible that there are still other protozoa capable of exciting pathological changes in the human body. The forms already recognized are representatives of all four classes of protozoa.

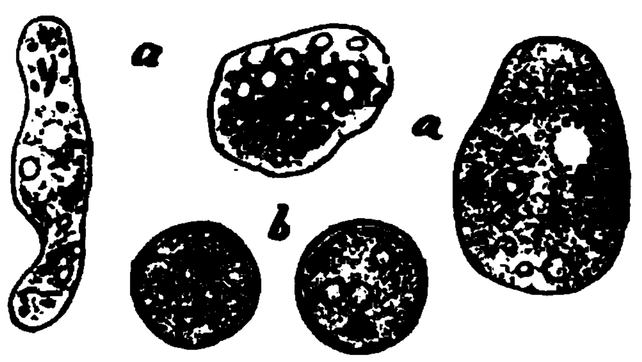

FIG. 523.—*Amœba coli mitis.* (After Roos.) *a*, Free motile amœbæ; *b*, encysted amœbæ. × 590.

Of the **Rhizopoda** there occur in the intestine three amœbæ, known as the *Amœba coli vulgaris*, the *Amœba coli mitis*, and the *Amœba dysenteriæ*. The Amœba dysenteriæ is certainly distinguishable from the other two, while the Amœba coli vulgaris and the Amœba coli mitis resemble each other very closely, and may possibly be identical.

The **Amœba coli vulgaris** is a harmless intestinal parasite which is not infrequently present in the intestine (Roos, Kruse, Pasquale). The **Amœba coli mitis** was observed by Roos and Quincke in cases of chronic enteritis in patients who had always lived in North Germany.

The Amœba coli mitis consists, according to Roos, of a protoplasmic cell-body, from 28–30 μ in diameter (in the spherical condition). It exhibits slow movements, and very frequently encloses foreign bodies, for example, bacteria and food-remains (Fig. 523, *a*). Besides the motile form, there occur, according to Roos, also encysted, spherical forms which are surrounded by a double-contoured membrane, and enclose clear, round vesicles in their interior (*b*). When fed to animals (cats) no pathogenic properties are disclosed.

The **Amœba dysenteriæ** (identical with the Amœba coli described by Loesch) has a diameter, according to Roos, of from 15–25 μ, but according to Kruse and Pasquale, from 10–50 μ. In the cell-body there may be recognized a homogeneous ectoplasm and a variable granular entoplasm, the arrangement of which varies according to the form of the animal (Fig. 524, *a*). By staining, a nucleus may be made visible within the cell. The cells are capable of active movement, and assume thereby the most varied shapes (*d*). They very often contain foreign bodies, particularly red blood-cells or remains of such (*b*), or are studded with

clear vacuoles (*c*). According to Roos, they may also become encysted (*e*).

According to investigations by Koch, Kartulis, Kruse, and Pasquale, they are invariably present in the dysentery prevailing in Egypt, and are usually also demonstrable in the dejecta. They have also been observed in cases of dysentery in Russia (Loesch, Massiutin), in America (Osler, Councilman, Lafleur, Lutz, Dock), in Germany (Roos), and in Austria (Kovacs). According to investigations by Kartulis, Councilman, Lafleur, Kovacs, Roos, Kruse, Pasquale, and others, it cannot be doubted that they are of some significance in the origin of certain forms of dysentery. It is only questionable whether they alone, or only with the aid of changes produced by bacteria, are able to bring about pathological changes. In support of the latter theory is the fact that, when present in the tissues, they are always accompanied by bacteria.

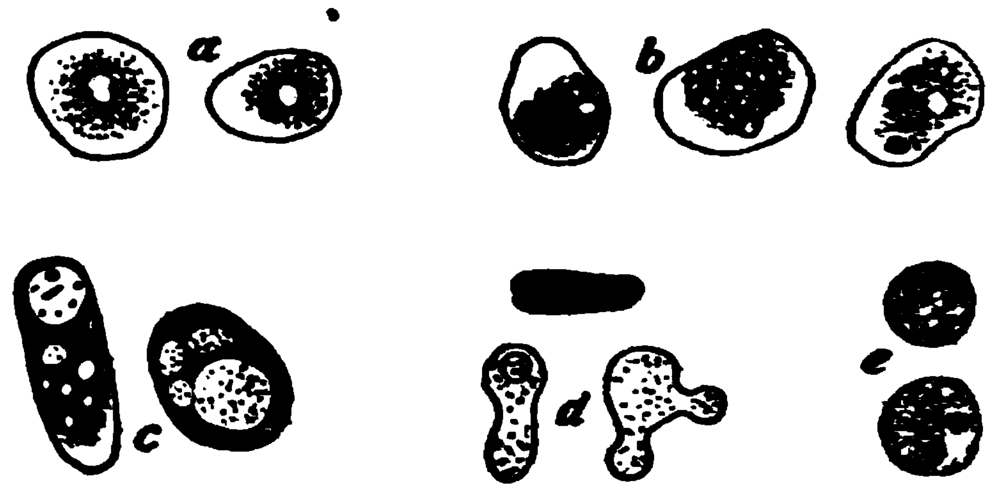

FIG. 524.—*Amœba dysenteriæ sive Amœba coli felis.* (After Roos.) *a*, Amœbæ without inclusions: *b*, amœbæ containing blood; *c*, amœbæ with large vacuoles in their protoplasm; *d*, young forms; *e*, encysted forms. × 665.

Amœbic dysentery is characterized by the occurrence of a hæmorrhagic catarrh, and by the formation of circumscribed ulcers with undermined edges. The amœbæ increase not only in the intestinal mucosa, but also penetrate into the mucosa and submucosa, and there form large colonies, in the region of which the tissue undergoes necrosis without the formation of any large amount of exudate. By the rupture of the submucosal foci through the mucosa there are formed ulcers with undermined edges, which, gradually increasing in size, may attain large dimensions.

If *abscesses of the liver* arise during the course of an amœbic dysentery, these may also contain the amœbæ in addition to bacteria; and it may be assumed that the former also take part in the destruction of the liver tissue.

The *amœbæ of dysentery are pathogenic for cats*, and, when fed to them or when introduced into the rectum of the animal, cause a rapidly progressive, often fatal dysentery, which is similar in all respects to amœbic dysentery in man. The amœbæ also penetrate into the mucosa and submucosa of these animals.

Von Leyden and *Schaudinn* ("Leydenia gemmipara," *Sitzber. d. K. Akad. d. Wiss.*, Berlin, 1896) found, in the fluid of two cases of ascites occurring in malignant disease of the abdomen, an amœba which consisted of colorless gelatinous cells, which put out pseudopodia, and showed a hyaline entoplasm and a granular ectoplasm. They were found chiefly lying together in groups.

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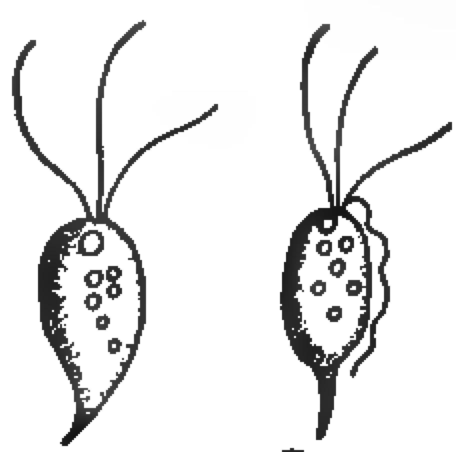
§ 184. A large number of species of the **Flagellates** (sub-class of the *Mastigophora*) occur in man, mammals, and birds, most frequently as

FIG. 525.—*Cercomonas intestinalis*. (After Davaine.)



A B

FIG. 526.—*Trichomonas hominis*, after Grassi (from Doflein).

FIG. 527. —*Trichomonas vaginalis* (from Doflein).

parasites of the body-passages accessible from without, but occurring also in the blood.

Cercomonas, Dujardin, a small flagellate (Fig. 525) with a flagellum

on the anterior end and a long-drawn-out posterior extremity, was observed by Kannenberg and Streng in gangrenous foci of the lung.

Trichomonas, Davaine, Braun (*Cercomonas intestinalis*, Lambl; *Trichomonas intestinalis*, Leuckart; *Monocercomonas hominis*, Grassi) is a pear-shaped flagellate, 4–10 μ long, with three flagella on the anterior end (Fig. 526).

Trichomonas hominis occurs in the small intestine of man, and has been observed particularly in pathological conditions of the intestinal tract (typhoid fever, cholera, intestinal catarrh, cancer of the stomach). It appears to be a harmless inhabitant of alkaline intestinal contents.

A B

FIG. 528.—*Lamblia intestinalis* (after Grassi and Schewiakoff). *A*, View from ventral surface; *B*, view from the left side.

Trichomonas vaginalis, Donné, is a flagellate very similar to the *Trichomonas hominis* (Fig. 527), and is often found in the human vagina. According to Miura, Marchand, and Dock, it may occur in the human urinary bladder.

Lamblia intestinalis (*Megastoma entericum*, Grassi; *Megastoma intestinalis*, Blanchard; *Cercomonas intestinalis*, Lambl; *Hexamitus duodenalis*, Davaine) is a turnip-shaped animal, having an indentation on the ventral surface (Fig. 528, *A*, *B*). It is about 10–16 μ long, and is found especially in the upper part of the small intestine, and has been observed in man, mice, dogs, cats, sheep, and rabbits. The parasite clings tightly to the epithelium of the intestine, but no pathological changes can be demonstrated in the underlying tissue.

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§ 185. Of the **Flagellates** that occur as **blood-parasites of man** the form known as **Spirochæte obermeieri** (discovered by Obermeier in 1873) has been known for some time, but formerly has been classed with the spiral varieties of bacteria (spirilla). The investigations of Schaudinn, however, make it appear very probable that the spirochætes are to be added to the protozoa.

Schaudinn's conclusions are not universally accepted. According to *Novy*, **Spirillum obermeieri** belongs to the bacteria and not to the protozoa, and he believes that the majority, if not all, of the spirochætes will be returned to their former place among the bacteria. *Sp. duttoni* and *Sp. gallinarum* have both been shown to be non-protozoal in nature.

The **Spirochæte obermeieri** (Fig. 529) is found constantly in the blood of patients suffering from **relapsing fever** during the attacks of the fever, and the multiplication of these organisms in the body is the cause of the disease.

The spirochæte is 16–40 μ long, and possesses numerous spiral turns. In a fresh drop of blood it shows very active motion. Carter and Koch succeeded in producing the disease in apes by inoculation with the spirochæte. The subcutaneous inoculation into apes of blood containing the spirochæte is followed after several days by an attack of fever, and the spirochæte is found in the blood during the febrile stage. The life history of the Spirochæte obermeieri is not known, but it may be similar to that of the spirochætes occurring in the blood of birds as studied by Schaudinn (see below). According to the autopsy-findings observed in man, the spleen is swollen and contains numerous yellow foci of degeneration, and often also anæmic infarcts.

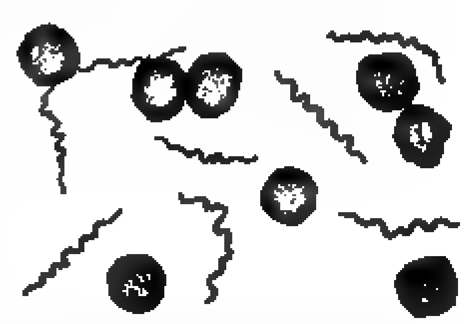

FIG. 529.—*Spirochæte Obermeieri* from the blood of an individual ill with relapsing fever. After a dried preparation stained with methylene blue. × 475.

According to investigations by Nikiforoff, the histological examination of the spleen shows extensive cell-necrosis and cell-degeneration (Fig. 530, *c*), as well as deposits of fibrin in the veins of the pulp, and proliferative processes in the pulp-cells. Further, numerous large pulp-cells (*f*) enclose red and white blood-cells or the remains of such. Finally,

FIG. 530.—Portion of tissue and isolated cells from a splenic follicle with partial necrosis, in relapsing fever. (After Nikiforoff.) (Potassium bichromate and sublimate, methylene-blue.) *a*, Free spirilla; *b*, lymphocytes with spirilla; *c*, non-nucleated lymphocytes; *d*, large, *e*, small mononuclear pulp-cells; *f*, phagocytes enclosing leucocytes and red blood-cells and their remains; *g*, free red blood-cells. × about 600.

numerous spirilla are found, especially in regions which are not wholly necrosed but contain degenerated and necrotic cells, in part free (*a*), and in part enclosed in leucocytes (*b*), partly well-preserved, and partly beginning to show disintegration.

According to Karlinski and Schaudinn, the infection is probably transmitted by bed-bugs.

Spirochætes have been observed also in birds, owls (Schaudinn), geese (Sacharoff, Gabritschewsky), and fowls (Marchaux, Salimbeni, Levaditi), and may cause epidemics in which great numbers of animals perish.

The **life-history of the Spirochætes** classed with the bacteria was not known until recently. Through the investigations of *Laveran* and *Schaudinn* it was for the first time determined that in their life-cycle there occurs an *alternation of generation and of host*. *Schaudinn* carried out his studies on the spirochætes found in the small owl (*Athene noctua*), which he named *Spirochæta ziemanni* (called by *Laveran* the *Hæmamœba ziemanni*). As a result of his investigations he believed that he had demonstrated the transmission of this spirochæte from the owl into the mosquito, *Culex pipiens*, in the intestine of which it passed certain stages of development, as described in the following paragraphs.

Within the owl there develop male and female individuals, the microgametocytes and the macrogametes. Copulation takes place in the intestine of the mosquito. From the fertilized macrogamete there develops an oökinete which produces in the intestine of the mosquito an enormous number of trypanosome-like offspring. These become transformed into true spirochætes, spread throughout the body of the mosquito, increase by longitudinal division, and wander into the œsophagus, whence, in the act of biting, they again pass into the blood of the owl. After an asexual period of multiplication in the form of spirochætes they again form gametes or sexual individuals in the blood of the owl. As the result of their distribution throughout the body of the mosquito the spirochætes may pass into the ovaries of the latter and thereby be transmitted to the next generation.

The fertilization in the intestine of the mosquito follows a ripening of the macrogametes (female cells) and the formation of microgametes (spermatozoa) from the microgametocytes. The oökinete resulting from the fertilization of a macrogamete is a worm-like body rolled up into a complicated skein. Through the grouping of the protoplasmic masses around the individual nuclei there are formed small trypanosome-like individuals having a characteristic flagellum-apparatus. Further, there may be developed both male and female individuals. The female forms are larger than the indifferent forms, their plasma is dark, the nucleus and blepharoplast relatively small, and the margin of the undulating membrane is not continued to form a flagellum. The males are very small and scarcely recognizable.

Through continued division the indifferent spirochætes in the intestine of the mosquito also become very small, so that single individuals can barely be made out.

Within the blood of the owl the spirochætes become parasites of the hæmoglobin-containing erythroblasts, in that they attach themselves to these by their posterior extremities. This is seen particularly in the bone-marrow and also in the spleen. After a certain time they form in the blood macrogametes and microgametes, which, on gaining entrance into the mosquito, again form new generations in the manner described. The *macrogametes* can also produce *new generations* in the blood without fertilization (parthenogenesis) and thereby *cause relapses*.

The above-given life-cycle of the spirochætes according to *Schaudinn* falls to the ground in the light of *Novy's* studies. The latter has shown that the *Spirochæte ziemanni* is not a spirochæte, but a trypanosome, and has no connection with the intracellular parasites of the owl's blood. Further, *Novy* regards *Sp. obermeieri* as belonging to the bacteria, basing his view upon his inability to demonstrate in the organism a nucleus, blepharoplast, undulating membrane, or flagellum of the protozoan type. On the other hand the spirilla of relapsing fever possess whips having all the characteristics of those of bacteria, divide transversely, multiply rapidly, resist changes in osmotic tension, show a greater resistance to heat than do the trypanosomes, excite the production of immune and germicidal bodies, and do not exhibit the aërotropism shown by trypanosomes.

In *relapsing fever we have most probably to deal with a group of closely related organisms* (*Novy*), which, while they may in one sense be regarded as distinct species, are derived from one stem. Five distinct strains of spirilla causing relapsing fever have been discovered: *Spir. obermeieri*, *Spir. novyi*, *Spir. kochi*, *Spir. duttoni*, and *Spir. carteri*. These differ from each other in the duration and severity of the initial attack, the fre-

quency and intensity of relapses, and in the mortality following an injection of a uniform dose of 0.25 c.c. of spirillar blood. The relapse is probably due to the survival of a few individuals that are more or less immune, so that a serum-fast strain develops. This in turn calls out a new antibody. If this is less active or more unstable, or more readily eliminated, the relapses will continue.

If *Schaudinn's* views on the protozoan nature of the organism found in syphilis (*Spir. pallida, Treponema pallidum*) are correct, that organism should then be classed here with the protozoa. At the present time this question cannot be regarded as settled, but it is most probable that the organism is of bacterial nature and should be classed, along with the spirochætes of relapsing fever, with the spiral forms of bacteria (*spirilla*). (See Syphilis.)

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§ 186. The genus **Trypanosoma** forms a second class of **blood-parasites** belonging to the **Flagellata**, found in man, mammals, and birds, and also in cold-blooded animals. Most authors place all the parasites of this class in the genus trypanosoma and distinguish different species. Doflein divides them according to the character of the flagella into three sub-genera: *Trypanosoma*, *Trypanomonas*, and *Herpetosoma*. Von Wasielewski classes only the blood-parasites of the frogs and fish with the trypanosomes, and would apply the name *Herpetomonas*, given by Kent, to the trypanosomes found in mammals.

Trypanosoma lewisi, Kent (*Herpetomonas, Trypanomonas, Trichomonas, Hæmatomonas*) is a very common parasite of rats. It is 8–30 μ long and 3–8 μ broad (Fig. 531), consists of a nucleated granular entoplasm and a delicate hyaline ectoplasm or periplastem, the latter forming an undulating membrane (Fig. 532, *c*) and a flagellum (*d*) which arises in the beak-like posterior end from a rod-like body and extends anteriorly along the edge of the undulating membrane.

The rod-shaped body (*b*) is designated micronucleus (Bradford and Plimmer), or nucleolus (Rabinowitsch and Kempner), or centrosome (Laveran and Mesnil), or blepharoplast (Von Wasielewski, Senn, Schaudinn). It has the significance of a nucleus and arises from the chief nucleus (Schaudinn).

The trypanosome infection occurs extensively among the rats of many regions. In other animals these trypanosomes do not appear to develop. The infected rats are apparently healthy, yet epidemics occur in which

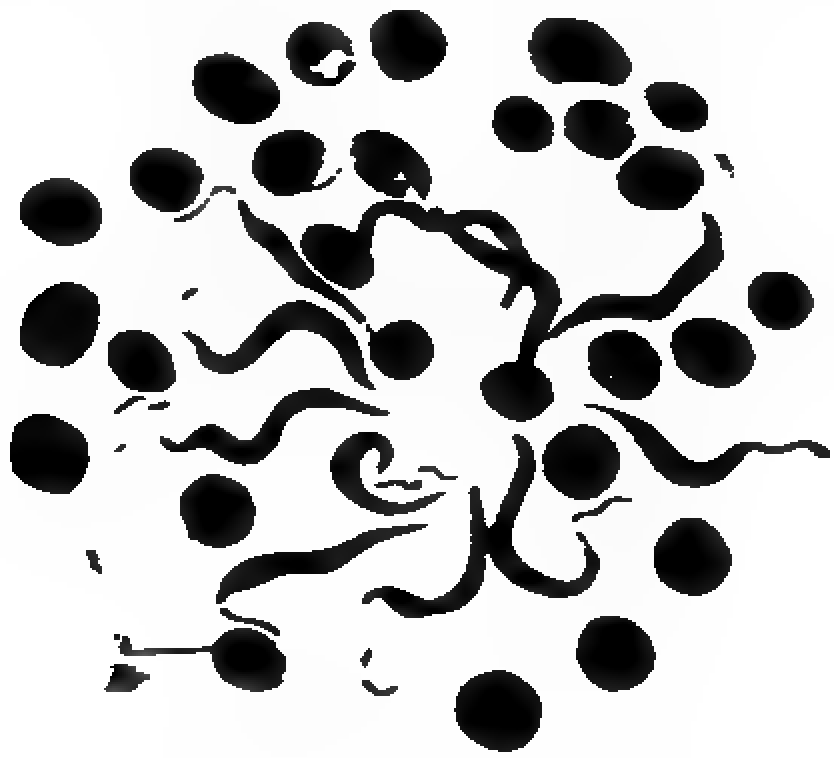

FIG. [illegible].—*Trypanosoma lewisi* from the blood of the rat. (From Doflein after Rabinowitsch and Kempner.) *E*, Erythrocytes.

great numbers of them die. Intraperitoneal inoculations of rats are followed by a multiplication of the trypanosomes, partly in the abdominal cavity and partly in the blood. According to Rabinowitsch and Kempner reproduction takes place partly by longitudinal and transverse division of flagellated individuals, and partly through the segmentation of large non-flagellated forms in which the cell-division is initiated by

FIG. [illegible].—*Trypanosoma (Herpetomonas) lewisi*, in different stages of development. (After v. Wasielewski.) *A*, Fully developed parasite with nucleus (*a*), rod-shaped body (*b*), undulating membrane (*c*), and flagellum (*d*); *B*, parasite with two nuclei and one rod-shaped body; *C*, parasite with [illegible] nucleus and two rod-shaped bodies; [illegible] parasites; *E*, parasite with four nuclei and four flagella; *F*, daughter-individuals still united into a rosette. × 2000.

a division of the nucleus by them designated as the chromatin framework, while new nuclei are snared off from the chromatin mass. According to von Wasielewski the chief nucleus (*E*) sometimes first divides, at another time the rod-shaped root of the flagellum or the blepharoplast (*C*); and the cells sometimes divide with two nuclei (*D*), and sometimes

after the formation of several nuclei and flagellum-roots (*E*, *F*), so that the resulting dividing flagellates remain for some time united into colonies. The natural infection of rats occurs probably through the medium of fleas and lice.

Trypanosoma brucei, Plimmer and Bradford, is very similar to *Tr. lewisi*, only the body is somewhat broader and the posterior end somewhat blunter. It is the cause of **Nagana** or the **tsetse-fly disease** of cattle, horses, antelopes, buffalo, donkeys, dogs, sheep, and goats occurring in Southern and Southeastern Africa, which is transmitted through the *tsetse-fly* (*Glossina morsitans*). The number of parasites in the blood may be very great; the infected animals suffer from fever and become anæmic; œdema develops in different parts of their bodies; further, there is also a conjunctivitis and the spleen is greatly swollen. The period of incubation is not more than nine days. The infected animals die after one and one-half to eight months.

It is also probable that the disease known as **Surra,** occurring endemically in horses, mules, camels, buffalo, cattle, and elephants in Dutch India, Indochina, and the Philippines, and which is transmitted by gadflies, is due to this trypanosome. It is likewise regarded as the cause of the trypanosome disease of horses and donkeys known as the coitus-disease or **dourine** occurring in Algiers, Southern France, Sumatra, Novarra, and the Pyrenees, and which is spread by coitus, and is inoculable into rabbits, rats, and dogs. Many authors regard the parasites found in these diseases as representing different species, giving to the first the name of *Trypanosoma evansi* and to the latter that of *Tr. equiperdum.* A variety of trypanosome found in Central South America and which causes the disease of horses known as *mal de caderas* is designated *Tr. equinum.* It is assumed that *Stomoxys calcitrans* acts as the agent of transmission of the parasite.

A variety of trypanosome known as *Tr. theileri* is found in cattle in South Africa and is inoculable only into this animal.

The occurrence of **trypanosomes in man** was first observed by Nepveu (1898). The investigations of recent years (Dutton, Todd, Boyce, Ross, Sherrington, Bruce, Castellani, Manson, Daniels, Laveran, etc.) have shown that trypanosome diseases occur also in man. The **sleeping-sickness of the negro** is now known to be due to a trypanosome infection. Castellani found the parasite in the cerebrospinal fluid of cases of sleeping-sickness, and his findings have since been confirmed by different observers. The disease occurs throughout tropical West Africa, and in recent years has spread throughout Central and Eastern Africa. Negroes are chiefly affected, but cases have also been observed in Europeans. The infection is transmitted by a biting-fly (*Glossina palpalis*). The parasites develop first in the blood, and during this period symptoms may be entirely wanting, or there may be attacks of fever. When the parasites gain access to the cerebrospinal fluid and there increase, cerebral symptoms, particularly coma, are produced as the result of a meningitis. The disease runs a chronic course and is invariably fatal.

Trypanosomes are found also in the disease known as **Gamba-fever** which occurs in Senegambia and the Congo, both in the natives and Europeans. According to Laveran, it is due to the same species of trypanosomes observed by Castellani in Uganda. Further, trypanosomes are believed to be the cause of the chronic disease known as **tropical splenomegaly,** which occurs in India, China, Arabia, Egypt, and Tunis, and is characterized by intermittent or remittent attacks of fever associ-

ated with a marked swelling of the spleen, leading after many months' duration to a progressive anæmia and cachexia having a fatal termination, and therefore distinguished from the ordinary malarial fevers by the designation of *cachectic fever.* It is very probable that the disease known as *Kala-azar* (black fever), which is widely distributed through the valley of Assam watered by the Brahmaputra, and is often characterized by dark discoloration of the skin, is related to tropical splenomegaly.

The **life-history of the trypanosomes** is similar to that of the spirochætes. According to investigations by *Schaudinn* the *Halteridia* (*Hæmoproteus noctuæ* of Celli and San Felice) of the little owl are the sexual stages of a trypanosome which multiplies in the common mosquito, *Culex pipiens*, so that after a complicated wandering through the body of the mosquito, through its bite again reaches the blood of the owl, in which after a period of asexual increase it changes into the familiar male and female Halteridia. The parasite must, therefore, be called the *Trypanosoma noctuæ.* Whether other members of the genus Halteridium or Hæmoproteus are to be classed with the trypanosomes remains to be settled. According to *Novy* (*Jour. of Infect. Dis.*, 1905) the observations of *Schaudinn* are open to an entirely different interpretation. He believes that the *Trypanosoma noctuæ* and the *Spirochæta ziemanni* of *Schaudinn* probably represent trypanosomes that have multiplied in the mosquito and are not to be considered as stages in the life-history of cytozoa. According to *Novy's* investigations trypanosome infection of birds is very widespread. With the trypanosomes there may be associated intracellular parasites, but no constancy can be shown to exist between a given trypanosome and a given cytozoon. The life-cycle of the trypanosomes and halteridia according to *Schaudinn*, as given in the following paragraphs, cannot, therefore, be accepted without question in the light of *Novy's* work.

If the male and female halteridia-stages enter with the blood of the owl into the intestine of the mosquito, the first forms the microgametocytes and microgametes, each of which penetrates into one of the pigment-containing macrogametes. As the result of this fertilization the latter become changed into oökinetes. Through a complicated metamorphosis proceeding from the nucleus the oökinete can become transformed into an indifferent trypanosome. The karyosome passing out from the nucleus, and which has the significance of a nucleus, moves to the right lateral border of the oökinete and forms there the blepharoplast of the trypanosome, that is, the structure which forms the undulating membrane and the flagella. The trypanosome thus formed can increase by longitudinal division.

The oökinetes can also form female trypanosomes which are plumper and show a more marked granulation than the non-sexual forms. The female trypanosomes represent permanent forms, and can produce new generations in the mosquito through parthenogenesis. Finally, the oökinete can also be transformed into a male trypanosome which is smaller and clearer than the female. Through heterotopous mitosis there may be formed in both the female and male trypanosome a small nucleus near the large one, and this may increase until as many as eight are formed. While in the female these are destroyed and only the chief nucleus is preserved, each of the eight nuclei develops in the male into a blepharoplast from which a minute male trypanosome arises.

The development of the microgametes in the blood of the owl takes place in the same manner as the formation of the male trypanosomes in the intestine of the mosquito, and they have the same structure as the latter. The indifferent trypanosomes passing from the mosquito into the blood of the owl are usually very small. They fasten themselves by their flagellated anterior end to the red blood-corpuscles; the flagellum apparatus then degenerates and the parasite takes on the appearance of a sickle-shaped, bean- or worm-shaped halteridium. When it has about doubled its size, it leaves its host and again develops a flagellum-apparatus, becoming changed again into a trypanosome. This is repeated several times until a certain size is attained; there then follows a multiplication through longitudinal division, the products of the division again seeking red blood-cells.

The fully formed female trypanosomes, the macrogametes in the owl's blood, are shaped like little worms; they penetrate the red blood-cells and deprive them of their hæmoglobin. They represent *permanent forms* and after a long interval can produce *new generations by means of parthenogenesis.* The male microgametocytes arise in the blood from indifferent forms and produce eight microgametes as in the intestine of the mosquito. The ripening of the macrogametes and their fertilization by microgametes take place in the intestinal tract of the mosquito.

It has not been positively decided at the present whether **human trypanosomiasis** is due to more than one variety of trypanosome. The different clinical course of the

affections makes this probable. In the forms known as *tropical splenomegaly* or *cachectic fever* and *kála-azár* there are found (*Leishman, Marchand*) in the spleen, liver, bone-marrow, lymph-nodes, and also in intestinal ulcers great numbers of small bodies, partly free and partly intracellular, consisting of an intensely staining ring-shaped chromatin body surrounded by a circular or oval, clear area staining lightly with eosin. Besides the chromatin-body there is often found also (*Marchand, Ledingham*) a small, intensely staining round or elongated granule, which is often connected with the chromatin-ring by a delicate stalk. These bodies (" *Leishman-Donovan bodies* ") were first found by *Leishman* and *Donovan* in smears made from the spleen, and were later studied by *Marchand, Ledingham, Manson* and *Löw, Bentley, Rogers*, and others, and were given different interpretations, the general opinion being that they represented degeneration forms of trypanosomes. *Rogers* has succeeded in growing them outside of the body and in demonstrating their transformation into elongated flagellated organisms resembling trypanosomes. On account of the absence of an undulating membrane *Rogers* believes the organism to be a herpetomonas. *Ross* regards it as a new genus and has called it *Leishmani donovani*. Nothing is yet absolutely determined concerning the transmission of this fatal infection. *Rogers* believes that it is transmitted by bed-bugs or mosquitoes. Very recently *Nicolle* (*Arch. de l'Inst. Pasteur*, Tunis; 1908) has succeeded in cultivating the Leishman-Donovan bodies from cases of *infantile splenomegaly* in Tunis. He regards the protozoön obtained as a new species, *Leishmania infantum*. The protozoa found in a case of tropical sore by *Wright* (*Jour. of Med. Res.*, 1903) and called by him *Helcosoma tropicum*, are regarded as Leishman-Donovan bodies, and designated by *Nicolle* as *Leishmania wrighti*. They are to be regarded as the infective agent of "Delhi boil."

According to the majority of writers *trypanosome* or *Gambian fever* is but the early stage of *sleeping-sickness*, both conditions being due to infection with the same parasite, the *Trypanosoma gambiense*. The first stage is of a variable duration, lasting from three months to three years or longer. During this stage there is a polyadenitis and the trypanosomes may be demonstrated in the blood and lymph-nodes. As a diagnostic method the examination of a drop of fluid removed from an enlarged cervical gland by means of a hypodermic needle is advised, since the parasites can be found in this way immediately if they are present in the body.

According to the views of many authors it is probable that **yellow fever** is a protozoan disease, although the parasite has not yet been demonstrated. *Schaudinn* showed that trypanosomes in certain stages formed such small individuals that *they* could not be recognized singly under the microscope. He would seek, therefore, the yellow-fever parasite among the flagellates. Yellow fever is endemic in the Antilles, Southern States of North America, Brazil, east coast of South America, and in many parts of West Africa. As the result of the work of a United States Commission consisting of *Reed, Carroll, Agramonte*, and *Lazear*, it was determined in 1900 that yellow fever is transmitted only through the bite of a mosquito (*Stegomyia fasciata*). Subcutaneous inoculation of the blood-serum of a case of yellow-fever into a non-immune during the first three days of the disease will transmit the infection. The mosquito, therefore, to become infected must suck the blood of a patient during this time. The bite of the mosquito does not become dangerous until twelve days after taking up infected blood, so that it is apparent that the parasite must undergo a further development within the body of the mosquito. The latter is able to infect after this period as long as it lives. *Novy* believes that the cause of yellow fever will be found to be a *spirillum*.

The first successful cultivation of a pathogenic protozoön and the demonstration of its relation to the disease by the injection of pure cultures were attained by *Novy* and *McNeal* in the case of *Trypanosoma lewisi* and later of *Tr. brucei*.

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§ 187. Of the **Sporozoa** occurring as parasites in man and in the mammals, the **coccidia** are to be mentioned first. In their young state they exist as non-encapsulated inhabitants of epithelial cells, particularly in those of the intestinal canal and its adnexa, the liver especially, and

FIG. 533. Section through the wall of a dilated bile-duct, filled with coccidia and lined with papillary proliferations. From a rabbit's liver that was studded with coccidia nodules (Müller's fluid, hæmatoxylin, eosin). *a*, Connective tissue; *b*, branching papillary proliferations covered with epithelium; *c*, coccidia. × 28.

more rarely in those of the organs of excretion. Some of the mature forms surround themselves with a capsule and become changed into round or oval *permanent cysts* or *oöcysts* (Schaudinn), which leave their resting-place and usually also their host, and under certain conditions form sickle-shaped *sporozoites* through the repeated division of their cell body (*sporogony*). Through the taking-up of sporozoite-containing oöcysts into a new host there is produced an infection of the latter, in that the sporozoites are set free and seek out epithelial cells for their further development.

Besides this form of multiplication there occurs within the infected organ also a reproduction by *schizogony*—that is, there are developed from mature but non-encysted individuals, by means of segmentation, a large number of new sickle-shaped individuals, the so-called *merozoites*, which seek out epithelial cells, and develop further in the same.

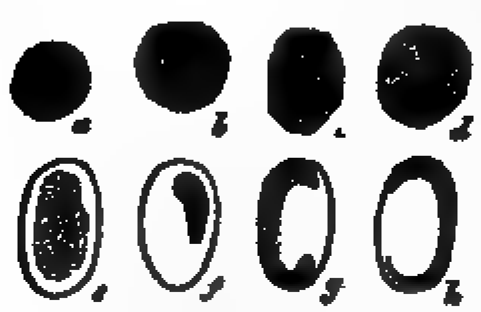

FIG. 534.—Coccidia from the biliary duct of the rabbit's liver (Fig. 533), showing different stages of development (Müller's fluid, hæmatoxylin). *a*, *b*, Small, coarsely granular young forms; *c*, *d*, large forms with darkly staining peripheral granules; *e*, *f*, *g*, *h*, oval, encapsulated forms, the protoplasm of which—partly coarsely granular and partly fine—fills up only a portion of the capsule. × 400.

Coccidium oviforme (Fig. 534) is a parasite of the intestine and biliary passages, occurring especially in rabbits. Künstler and Pitres found similar coccidia in man in a pleuritic exudate. Podwyssozki claims to have observed them in the human liver.

In the liver of rabbits the invasion of coccidia leads to the formation of white nodules which may reach the size of a hazel nut, and are designated as *coccidia-nodules*. These nodules contain a soft, white, or yellowish-white mass, and consist essentially of

dilated bile-passages, the inner surface of which is more or less richly furnished with papillary growths (Fig. 533), and whose lumen contains great numbers of coccidia.

The coccidia occur in the bile-passages partly in the form of non-encapsulated protoplasmic structures, and partly in the form of encapsulated bodies. The smallest coccidia, which are regarded as the younger forms, exhibit a coarsely granular protoplasmic structure (Fig. 534, *a*, *b*), within which a nucleus (*a*) may occasionally be demonstrated. The larger forms exhibit on their outer surfaces regularly arranged granules (*c*, *d*), which stain intensely with hæmatoxylin. The encapsulated forms occur as oval, doubly contoured, clear bodies (*e*, *f*, *g*, *h*) within which lies a variously shaped mass exhibiting also various forms of granulation, but never entirely filling up the space within the capsule.

To the coccidia belong probably also those **parasites** which **occur in the epidermis of man** and form there peculiar growths known as **epithelioma contagiosum** (Fig. 535). In its fully developed condition the growth consists of a small nodule, about the size of a pea or larger, which is elevated above the surface of the skin, shows a small groove in its centre, and possesses a waxy lustre.

On section there may be seen a lobulated epithelial growth (Fig. 535, *d*), with a central cavity opening externally (*g*), thus forming a growth resembling a gland; and it has been many times mistaken for a hypertrophic sebaceous gland. It therefore represents an independent new-formation of epithelium due to a parasite. The parasites develop inside of the epithelial cells of the lobulated growth (*e*), but are pressed by the

FIG. 535.—Epithelioma contagiosum. Section through greatest diameter (Müller's fluid, hæmatoxylin). *a*, Epidermis; *b*, connective tissue; *c*, sebaceous gland; *d*, gland-like epithelial proliferations; *e*, parasites; *f*, horny cells mingled with parasites; *g*, duct filled with horny epithelium and parasites. × 12.

growth of the adjacent epithelium toward the central cavity of the new-formation (*f*), and lie there in a meshwork of desquamated and horny epithelial cells.

The earliest stages of development of the parasites occur in the epithelial cells as small protoplasmic bodies (Fig. 536, *a*, *b*), which can be distinguished from the cell-protoplasm only with difficulty; occasionally they contain in their interior small, distinct granules, and are therefore more evident. Later they increase in size, and finally fill up completely the epithelial cell (*c*, *d*, *e*), pressing the nucleus to one side. At the same time the granules within the cell (*c*) increase, and grow to larger bodies, so that the parasite finally becomes divided into a greater or less number of well-defined structures (*d*, *e*, *f*) lying in a finely granular

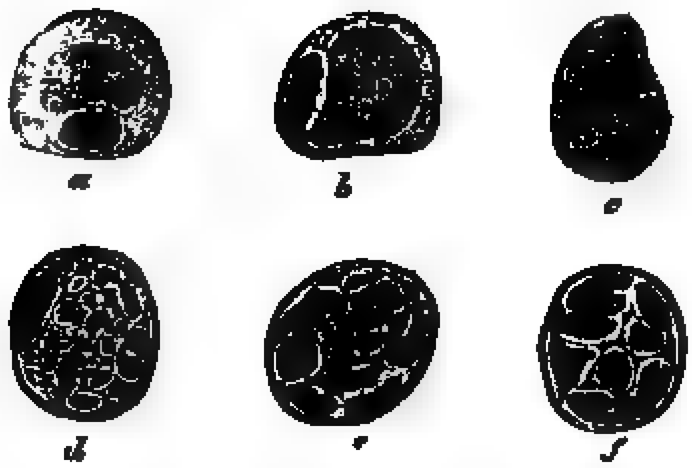

FIG. 536.—Parasites of Epithelioma contagiosum in various stages of development, lying inside epithelial cells (Müller's fluid, hæmatoxylin). *a*, *b*, Epithelial cells, enclosing a protoplasmic body inside of which lie single large granules; *c*, epithelial cell almost completely filled with parasites; *d*, *e*, *f*, parasites completely filling the epithelial cells, and divided into numerous separate bodies lying in a granular network; the cell-nucleus has been destroyed in *f*. × about 600.

network. The nucleus of the epithelial cell is destroyed during this time.

The epithelial cells which enclose parasites develop early a distinct membrane, which becomes more and more clearly defined, and surrounds the parasite. The parasites which are expelled from the cells form oval bodies which appear enclosed in a capsule and present a homogeneous appearance. They stain deeply with hæmatoxylin.

The contagious epitheliomata may appear in great numbers in one and the same individual, and several persons living together may be either simultaneously or successively attacked. The spread of the disease is therefore referred to a contagion.

By many writers the molluscum bodies are not believed to be parasites, but are regarded as hyaline or horny products of cell-degeneration.

Our knowledge of the significance of the so-called **Miescher's sacs** is still incomplete. They are tube-shaped structures which are not infrequently found in the muscles of the hog (Fig. 537, *a*, *b*), cattle, sheep (especially in the œsophagus), and mice. They vary in size, and lie within the muscle-fibres. In mature parasites the contents of the tubes are differentiated into single segments defined by a membrane (Fig. 537), which enclose spherical (*c*), kidney-shaped, or sickle-shaped bodies. The parasite is classed with the **Sarcosporidia.** The separate segments are designated *sporocysts* or *sporoblasts,* since within these the round or sickle-shaped *spores* (*Rainey's bodies*) arise. From the latter,

a

b

FIG. 537.—Miescher's sacs, from swine-muscle. *a*, *b*, Muscle cut longitudinally and transversely. × 100. *c*, Longitudinal section. × 580.

new Miescher's sacs may develop under favorable conditions (Pfeiffer). Ingestion of meat containing sarcosporidia is not dangerous for man, but

sarcocysts have been observed in man in the muscles, heart, intestine, and liver (Lindemann, Koch, Kartulis, Rosenberg, and others).

As early as 1870 *Eimer* published observations of the development of coccidia, but their life-history has been accurately determined only in recent years, through the investigations of *R. Pfeiffer, Simond, Léger, Schaudinn, Schuberg, Siedlecki, Schneider, von Wasielewski, Labbé*, and others.

The **reproduction of coccidia** occurs (*Lühe*) partly through *sporogony*, partly through *schizogony*. The first method serves for the spreading of infection and the preservation of the species, the second increases the extent of the infection within the infected host. *Sporogony is closely connected with a previously occurring copulation* which in its course suggests the fertilization of the egg of the metazoa. An *alternation of generations* also takes place.

FIG. 538.—Cycle of development of *Coccidium Schubergi*. (After Schaudinn and Lühe). *1*, Sporozoite (or merozoite) penetrating into an epithelial cell; *2*, mononuclear schizont in an epithelial cell; *3*, multinuclear schizont; *4*, division of the schizont (schizogony) into numerous merozoites; *5*, macrogamete (female cell) arising from a merozoite; *6*, fully developed macrogamete surrounded by extruded chromatin granules; *5a*, microgametocyte (male cell) arising from a merozoite: *6a*, microgametocyte surrounded by loosened microgametes (spermatozoa); *7*, fertilization of the macrogametes by microgametes; *8*, young oöcysts; *9*, oöcysts with sporoblasts; *10*, oöcysts with sporocysts, each containing two sporozoites; *11*, sporozoite.

The development and reproduction take place in the following manner: In schizogony the sickle-shaped germ (Fig. 538, *1*) arising as a *sporozoite* or *merozoite* develops within an epithelial cell into a schizont (*2*) in which there soon takes place a multiplication of the nucleus (*3*). There then results (on the second day after the over-feeding of sporocysts) a formation of merozoites (*4*) corresponding in number to the nuclei, and a residual body which is left behind after the segmentation.

The merozoites again seek epithelial cells, and the same development begins anew. If the affected organ, as the result of these processes, becomes overcrowded with parasites, there are then formed sexual individuals (*Schaudinn*). Some of the merozoites grow into large cells, the *macrogametes* (*5, 6*) or female cells, which when mature throw off a portion of their chromatin-substance (*6*), and either remain naked or surround themselves with a capsule, which is provided with a micropyle. At the same time other merozoites develop into the male sexual cells or *microgametocytes* (*5a, 6a*), the nuclei of which divide into many daughter-nuclei. The latter approach the surface of the cell, and, surrounded by a certain amount of protoplasm, are constricted off. (6a)

and then represent the *microgametes* (corresponding to the spermatozoa of the higner animals). The *copulation* of the microgametes with the macrogametes takes place in a manner similar to that of the fertilization of the metazoan egg, in that the microgamete penetrates the encapsulated form of macrogamete through the micropyle, and the naked form through a certain point which pushes itself outward to form a prominence (7), the conceptional protuberance. *Sporogony* follows the fertilization—that is, the oöcyst (*8*) is formed, in which, through the division of the nucleus and protoplasm, there arise four *sporoblasts* (*9*), each of which later produces two sickle-shaped *sporozoites* (*10*).

Numerous authors hold the view that other local pathological conditions of the tissues in man than those described above may be referred to *sporozoa*, particularly *carcinoma*, *Darier's disease*, *Paget's disease*, peculiar diseases of the urinary passages, etc. It may, however, be remarked that this assumption in part is based upon error, and in part has not been absolutely proved by the investigations which have been made up to the present time.

So far as *carcinoma* is concerned, in spite of the great number of works on the subject, so numerous indeed that they can scarcely be perused (cf. § 121), no proof has yet been given that protozoa, coccidia in particular, are present within the epithelial proliferation and are to be regarded as the cause of the same. All the appearances described as occurring in carcinoma cells, even the sickle-shaped formations which have been thought to be convincing and those provided with a sort of capsule, may be otherwise interpreted, and may be explained in part as changed nuclei, in part as altered protoplasm of the cancer-cells, in part as cell excretions, and finally in part as a product of cell-fusion or of the taking up of leucocytes by the cancer cells.

The disease described by *Darier* as *psorospermose folliculaire végétante*, and referred by him to the presence of sporozoa, is very probably only an inflammatory affection of the skin characterized by a pathological cornification (keratosis follicularis of *von Withe*), in which little horny plugs and pegs are developed successively in the epithelium of certain parts of the body, while the cutis shows slight inflammatory changes. According to *Buzzi*, *Miethke*, *Rieck*, *Kröning*, *Petersen*, and others, the "*corps ronds*," described by *Darier* as parasites, contain kerotohyalin and eleidin, substances which are present in cornified cells but not in gregarinæ.

Paget's disease is an affection spreading from the nipple, beginning with an eczema-like inflammation, and leading to superficial ulceration, and finally ending in a carcinomatous infiltration of the skin. It has been referred by *Darier*, *Wieckham*, *Malassez*, and others to the presence of a parasitic sporozoon in the epithelial cells; but is, however, either an eczema arising from other causes, and finally leading to cancer, or else is a primary cancer accompanied by inflammatory processes (*Ehrhardt*), in which peculiar changes take place in the epidermis, particularly swelling of the protoplasm and nuclei, with formation of vacuoles, and further proliferative changes, the peculiar appearances of which might be mistaken for parasites. According to *Jacobaeus* these appearances are brought about through the penetration of the carcinoma into the superficial epithelium.

In **variola** and **vaccinia** there occur constantly in the epithelium that has undergone recent changes small lightly staining bodies surrounded by a clear zone, often in great numbers. Their constant occurrence in repeated inoculations and their characteristics make it very probable that they represent parasites belonging to the protozoa, and this view is favored by numerous authors (*Guarnieri*, *E. Pfeiffer*, *L. Pfeiffer*, *Bosc*, *Funk*, *Councilman*, *von Wasielewski*, and others). *Hückel* and *Borrel* have attempted to interpret these structures in another way.

Negri ("Etiologie der Tollwut," *Z. f. Hyg.*, 43 und 44 Bd., 1903) describes **small bodies** found in the nervous system of dogs inoculated subdurally with the **virus** of **rabies** which he regards as protozoa and considers to be the cause of rabies. Investigations by *Volpino* ("Struttura dei corpi descr. da Negri nella Rabbia." *A. per le Sc. Med.*, xxviii., 1904) and by *Luzzani* ("La dimostraz. del Parass. specif. in un caso di rabbia nel l'uomo." *Ibid.*) support the view of *Negri*, but offer no further information as to the nature of the parasite. According to *A. W. Williams*, the Negri bodies possess a definite chromidium and are, therefore, to be classed with the rhizopods (*Journ. of Infect. Dis.*, 1906).

Mallory ("Scarlet Fever." *Jour. of Med. Res.*, x., 1904) has found a protozoön-like body in four cases of **scarlet fever**. *Field* (*Journ. of Exper. Med.*, 1905) believes that these bodies are products of degenerating tissue-cells and leucocytes. *Gotschlich* ("Protozoenbefunde im Blute von Flecktyphuskranken." *D. med. Wochenschr.*, 1903) found pear-shaped bodies in six cases of **typhus fever** which resembled the parasites of Texas fever, and in four cases he found also flagellated bodies.

According to *Hess* and *Guillebeau*, coccidia may occasion in young cattle diseases of the intestine resembling dysentery. According to *Olt* and *Voisin*, the shotty eruption of swine characterized by the formation of little cysts in the skin is caused by coccidia (*C. fuscum*), but according to *Lühe* the description of the parasites does not correspond to coccidia.

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§ 188. Under the designation **Plasmodium malariæ** (Marchiafava and Celli) or the **hæmosporidia of malaria** are grouped together at the present time all those blood parasites which are regarded as the cause of human malaria. The parasites are found in the blood of malarial patients in different forms, usually enclosed in cells; and, according to the observations of Golgi, Celli, Marchiafava, and others, a definite relation can be demonstrated between the number and the stage of the development of the parasite and the attacks of fever. The parasites pass through different stages of development in the interval between the attacks of fever, these stages, according to the authors mentioned, differing in *febris quartana*, *febris tertiana*, and *febris quotidiana*. At the same time the parasites of the different forms of fever exhibit certain differences in their physiological characteristics. Supported by these facts, there may there-

fore be distinguished in man different species of the malarial plasmodium. In its narrower sense the designation *Plasmodium malariæ* is used only with reference to the parasites of quartan fever. The parasite of vernal tertian on account of its active movements is known as *Plasmodium vivax* (Grassi and Feletti); and the parasite of tropical malaria, which in Italy appears in the autumn, is designated *Plasmodium præcox*.

Schaudinn's classification of the malarial parasites is accepted by most writers. He recognizes three varieties: *Plasmodium vivax* (tertian), *Plasmodium malariæ* (quartan), and *Plasmodium immaculatum* (æstivo-autumnal parasite).

The development and increase of the plasmodia take place within the red blood-corpuscles, in which, first of all, small, colorless amœboid bodies (Fig. 539, *a*) appear. In *quartan fever* the further development of the parasite proceeds by an enlargement of the small amœboid forms (Fig. 539, *a*, *b*, *c*, *d*, *e*), so that the red cell becomes more and more filled

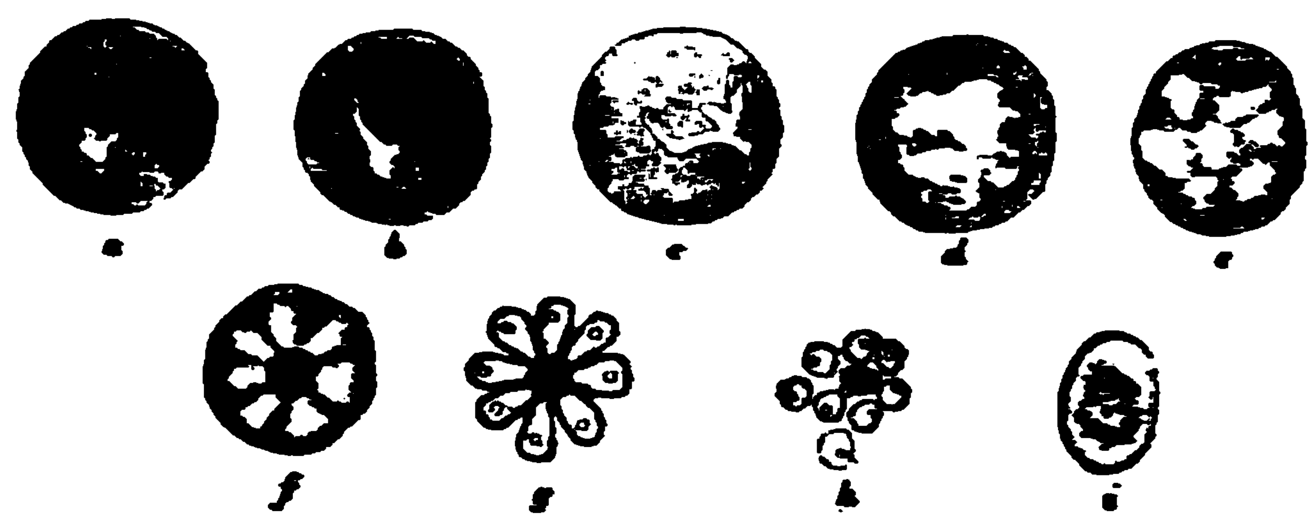

FIG. 539.—*Plasmodium malariæ* of quartan fever, in different stages of development. (After Golgi.) *a*, Red blood-cell with a small non-pigmented plasmodium; *b*, *c*, *d*, *e*, pigmented plasmodia of varying size inside the red blood-cells; *f*, plasmodium in beginning segmentation, with centrally placed pigment; *g*, segmented plasmodium; *h*, plasmodium divided into separate spherules; *i*, free gamete (sexual individual).

up by the parasite. At the same time pigment-granules appear within the bodies of the plasmodia. When the plasmodia have attained a certain size, the pigment-granules move toward the centre, while at the same time a radiating cleavage sets in, so that daisy-like figures ("*rosettes*") (*f*, *g*) are formed, which consist of a pigmented centre and non-pigmented, radiating club-shaped petals. Later the clubs become detached from the central mass of pigment and take on a circular form (*h*).

According to Golgi, the development and division of the plasmodia of quartan fever require three days for their completion, and the attacks of fever coincide with the division of the plasmodia. The red cells occupied by the parasites are destroyed; the young plasmodia just formed by division penetrate again into blood-corpuscles, and the cycle of development begins anew. The pigment-granules formed by the plasmodia are taken out of the circulating blood partly free and partly enclosed in cells, and deposited in different organs, particularly in the spleen, liver, and bone-marrow.

In *febris tertiana* (*vernal tertian*) the cycle of development is completed in two days. The plasmodia developing within the red cells (Fig. 540, *a*–*d*), which are designated *Plasmodium vivax*, show much livelier motion and lead much more quickly to a decolorization of the red blood-corpuscles than those of quartan fever, so that the red cells become decolorized on the first day after the fever, while the plasmodia are still small. The protoplasm of the plasmodia of tertian fever is also more delicate and less sharply contoured and the pigment-granules are smaller. In its

division each plasmodium splits up into from fifteen to twenty new cells (*e*), while the parasite of quartan fever forms only from six to twelve. According to Celli and Marchiafava, sporulation not infrequently occurs prematurely, from five to ten spores arising within a red corpuscle.

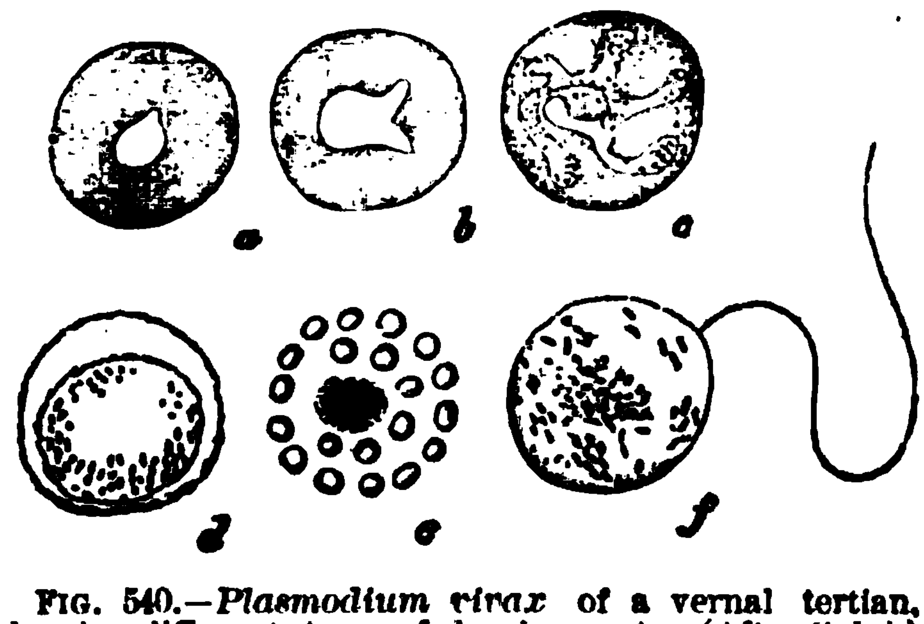

FIG. 540.—*Plasmodium vivax* of a vernal tertian, showing different stages of development. (After Golgi.) *a*, First stages of development; *b*, *c*, enlarged plasmodia with pseudopodia; *d*, plasmodia before sporulation, the red blood-cell decolorized; *e*, sporulation; *f*, free parasite with flagellum (microgametocyte).

The parasite of tropical or *pernicious malaria*, the *Plasmodium præcox*, differs from the hæmosporidia of the vernal fevers, particularly in the fact that it is much smaller (Fig. 541, *a*, *b*, *c*, *d*) and executes lively movements within the red cells. It completes its life-cycle in twenty-four to forty-eight hours. Through the formation of a central vacuole it often appears in the form of a ring. During the stage of multiplication the parasite collects in the internal organs, so that the division-figures (*d*) must be sought in the spleen, liver, bone-marrow, and brain (where they are present in great numbers). Some of the infected red cells become crenated and prickly, and of a brassy color (Marchiafava, Celli); they die prematurely, and blood-cells which contain no parasites are also destroyed. The attacks of fever can in the case of autumnal tertian fever become so prolonged that they pass into one another, and the condition thereby assumes the character of a *sub-continuous* or *continuous fever*.

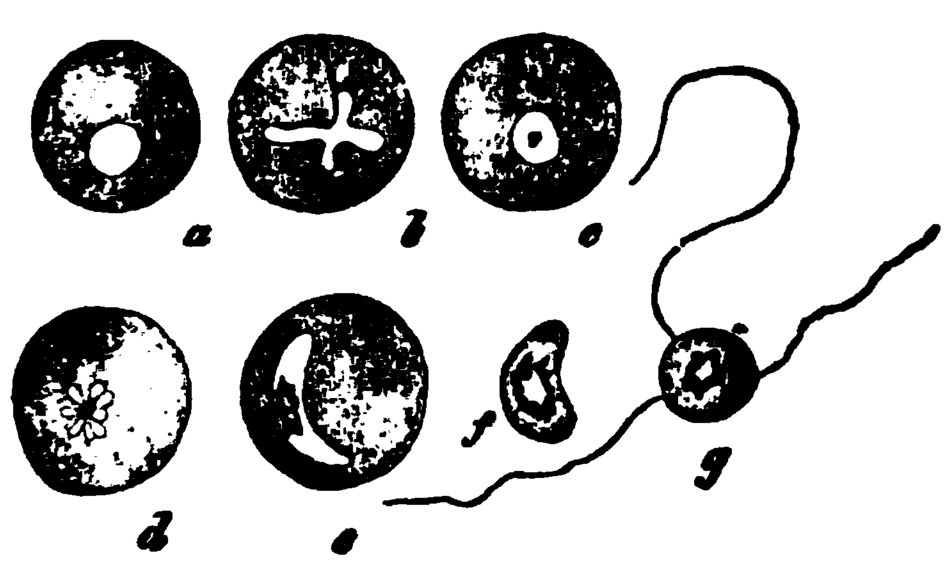

FIG. 541.—*Plasmodium præcox* of tropical malaria, showing different stages of development. (After Golgi and Sanfelice.) *a*, First stages of development; *b*, plasmodia with pseudopodia; *c*, round plasmodium with pigment, before segmentation; *d*, sporulation; *e*, intraglobular sexual individual; *f*, *g*, free sexual cells.

According to Marchiafava and Celli, there also occurs a quotidian parasite very similar to the latter, but producing no pigment at all.

Nuclear bodies may be demonstrated, during certain stages of development, in the protoplasm of all the endoglobular forms of malarial hæmatozoa. According to Ziemann, in *sporulation* there first occurs a *division of the chromatin into small clumps*, and then later the division of the cell-body, so that every clump of chromatin is surrounded by a zone of protoplasm.

Besides the forms of development already described which lead to an intracellular increase of the plasmodia through *schizogony*, there occur particularly extraglobular, in part also endoglobular, round and oval, sickle- or crescent-shaped structures (Figs. 539, *i*; 541, *e*, *f*), as well as round bodies with flagella (Figs. 540, *f*; 541, *g*), which also contain a nucleus and pigment. The crescent forms occur particularly in the pernicious fever (Fig. 541, *e*, *f*). Celli regards them as a diagnostic feature of this form of fever; and Ziemann also holds that typical crescents are not formed in the other varieties of malaria.

The last-named forms Laveran had already described as structures belonging to the cycle of development of the plasmodia, while Golgi, Canalis, Celli, Marchiafava, Bignami, Bastianelli, Ziemann, and others regarded them as sterile vegetation-forms that die without further development. First through the investigations of Manson, Bignami, Ross, and MacCallum, to which were later added those of Grassi, Bastianelli, Bignami, Celli, Laveran, Koch, Schaudinn, and others, it was shown that the *crescents*, the *oval bodies*, the *spherical bodies*, or *spheres*, as well as the *flagellated bodies* known as *polymitus*, *are intended for the reproduction of the parasites by copulation*. The flagella-producing hyaline spheres arising from the crescents are *male sexual individuals* or *microgametocytes*, and the flagella developing from them, in whose formation the chromatin of the cell takes an essential part (Sacharoff), have the significance of *male sexual cells*, *spermatozoa*, or *microgametes*; while the non-flagellated spheres arising from the granular crescents have the significance of *female sexual cells* or *macrogametes*. The crescents leading to the formation of the sexual cells appear only after the infection has lasted for several days. In the chronic cachexia following malaria the forms leading to schizogony are absent, and the crescents alone are present.

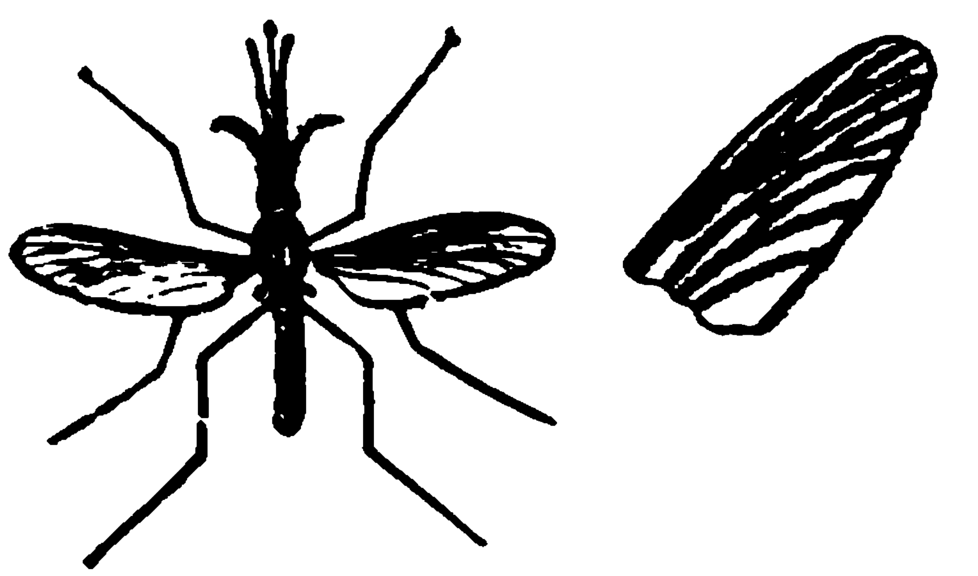

Fig. 542.

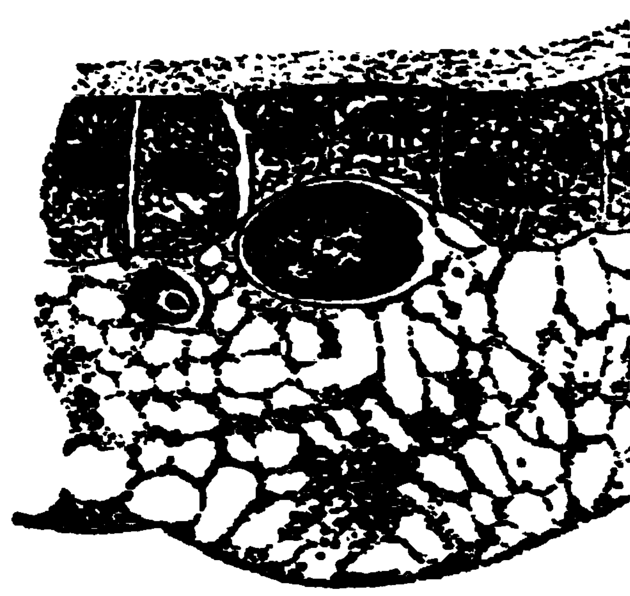

Fig. 543.

Fig. 542. *Anopheles claviger*. (After Meigen, *loc. cit.*) × 4. To the right a wing at higher magnification.

Fig. 543. Oöcysts of human pernicious malaria (*Plasmodium præcox*) in the intestinal wall of a mosquito. (After Grassi.)

The *copulation of the malarial parasites* of man takes place normally in the *stomach of the mosquito*, in different *species of Anopheles* (Fig. 542), which take up the malarial parasites during the sucking of blood from malarial patients.

The copula arising from the union of the macrogamete and microgamete is designated *oökinete* (Schaudinn), a long, motile structure (described earlier as vermiculus by Danielewsky) which penetrates into the stomach wall of the mosquito (Fig. 543), where through the formation of a capsule it becomes the *oöcyst*. The latter then enlarges and forms numerous daughter nuclei, and then *sporoblasts*, which break up into the *sporozoites* (Fig. 544) and the residual body. According to Grassi, as many as 10,000 sporozoites may be formed in one oöcyst.

The sporozoites, which are formed in enormous numbers, pass into the body-cavity after the rupture of the oöcyst, and collect principally in the salivary glands, and through the bite of the infected mosquito are again transmitted to man, in whose blood they multiply within the red blood-cells through schizogony.

The *pathogenic significance of the malarial plasmodia* rests in the first place upon the destruction of red blood-cells. In the pernicious form this may be so extensive that hæmoglobinuria may take place. The melanotic pigment formed in the parasite is a product of the vital activity of the parasites. In addition, as the result of the destruction of hæmoglobin, there occur deposits of hæmosiderin in the bone-marrow, spleen, liver, and occasionally also in the kidneys. In the case of a marked destruction of the red blood-cells there may occur an excretion of dark red urine, a hæmoglobinuria (*black-water fever*). The massing of the parasites of pernicious malaria in the cerebral capillaries may cause circulatory disturbances with the occurrence of numerous hæmorrhages, and consequent severe cerebral symptoms (perniciosa comatosa, soporosa, apoplectica, meningitica).

As the result of the retention of pigment-containing malarial parasites and the deposit of the products of blood-destruction, there occurs a marked swelling of the spleen associated with hyperæmia, followed in part by tissue-degenerations and in part by tissue-proliferations.

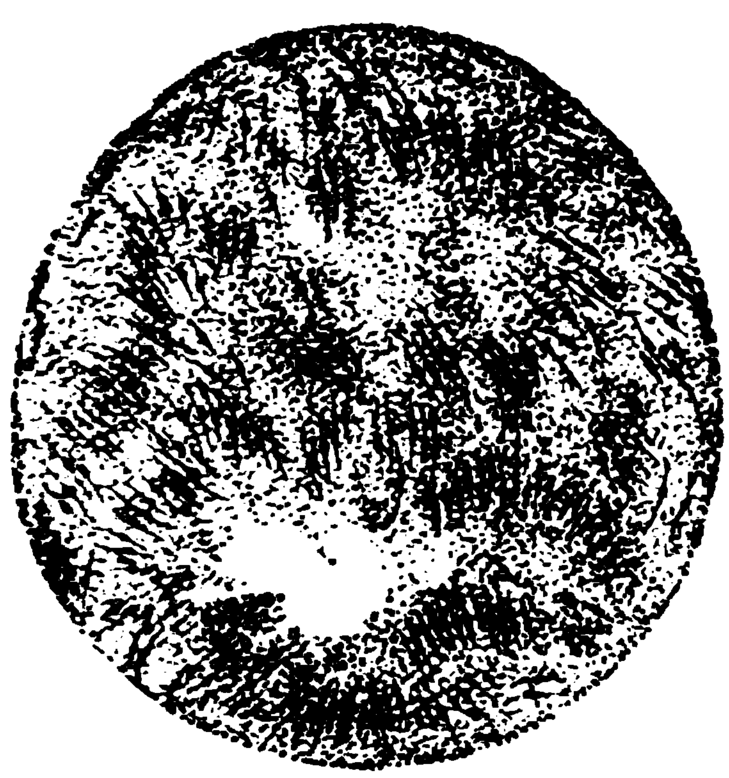

Fig. 544.—Oöcyst of *Plasmodium præcox*, filled with sporozoites. (After Grassi.)

After a long duration of the process the spleen may become markedly enlarged, pigmented, and greatly changed in structure. Likewise, in the liver there may be found in part degenerations and pigmentations, and in part also indurative proliferations.

Certain varieties of the plasmodium correspond to the individual types of fever, as given above, but it must be noted that the fever-forms known as quotidian, subcontinuous, and continuous ("*comitata*"), may also arise through the presence in the blood of different generations of the plasmodia of tertian or quartan fevers, so that daily a portion of the parasites comes to sporulation. In this way there arise quotidian forms of fever, which must be regarded as a double tertian infection or as a triple quartan.

According to the investigations by Schaudinn, the *relapses* that occur sometimes weeks and months after the original attack may be explained by the fact that the macrogametes, which are longer-lived, revert to schizonts by throwing off a portion of their nucleus and protoplasm. According to Plehn, basophile granules are found in the red blood-cells as long as the infection persists. They vanish when the infection finally comes to an end.

The malaria occurring in northern countries corresponds in general to the vernal forms of Italy, while the æstivo-autumnal form is found in the tropics.

Hæmosporidia—that is, sporozoa which live at the cost of the red blood-cells, and thereby produce diseases which are to be classed with malaria—occur very frequently **in animals.** Those of **birds** are best known (*Danilewsky, MacCallum, Ross, Grassi, Dionisi, Celli*, and *Schaudinn*) and the life-cycles of the hæmosporidia of the pigeon, owl, and skylark have been determined. *Labbé* distinguishes two genera in birds, *Halteridium* and *Proteosoma* (*Hæmoproteus* of *Kruse*); as to the number of undifferentiated species, nothing can be said at the present time. *Celli* obtained from the birds men-

tioned three well-defined species. *Schaudinn* assigns the parasites of birds designated as proteosoma to the genus plasmodium.

Of the **Mammalia**, cattle in particular suffer in different countries (Southern States of North America, Italy, South Africa, Roumania) from a malaria characterized by high fever and hæmoglobinuria. In the malaria of cattle known as *Texas-fever*, *Smith* and *Kilbourne* found in the red blood-cells a small, often pear-shaped, and paired parasite (*Piroplasma bigeminum*), whose pathogenic significance they determined through the inoculation of healthy cattle with blood containing the parasites. *Babes* found the same parasite in the epidemic **hæmoglobinuria of cattle** prevalent in Roumania. The first-named observers showed further that the natural infection takes place through parasitic ticks (*Boöphilus bovis*) living upon the cattle, the infection being transmitted, not by the same tick which takes up the infected blood, but only through the generation descending from the same. This mode of infection was confirmed by *Koch* in the hæmoglobinuria of cattle occurring in German East Africa and by *Grassi* in that occurring in cattle in Italy. The mode of development of the *piroplasma* in the body of the tick is still unknown; and it therefore cannot be decided whether the parasite should be classed with the known malaria parasites. Against a near relationship with the latter speaks the fact (*Lühe*) that it increases within the red blood-cells by a repeated simple division. According to *Kolle*, there occurs in South Africa, besides Texas-fever, another malarial disease of cattle (*Febris malariaformis*), which is caused by an endoglobular parasite. *Theiler* also distinguishes two forms of piroplasmosis of cattle in South Africa. The piroplasma occurring in dogs and in horses he regards as an especial form distinct from Piroplasma bigeminum. According to observations by *Nocard* and *Almy* and *Motas* a piroplasmosis associated with hæmoglobinuria is not uncommon in dogs in France. According to *Galli*, *Valerio*, and *Piana*, it occurs also in Italy.

According to *Bonome* and *Celli*, hæmosporidia also cause malaria in *sheep* and *lambs*, according to *Koch* and *Kossel* also in apes, and according to *Dionisi* in bats; but the life-history of all these parasites is unknown.

Danilewsky and *Celli* have described hæmosporidia in the *frog*, and the latter observer determined also the development of the parasite in the blood.

Whether the malarial parasites of man can be transmitted to animals, or whether the malaria of animals can lead to an infection of man through the medium of mosquitos, is not decided with certainty, but appears improbable. The plasmodia of the bat most closely resemble those of man, yet attempts at inoculation made by *Dionisi* gave no positive results. It may therefore be assumed that malaria would die out in a given region, either when all susceptible anopheles were killed, or all infected human individuals healed or protected from mosquito bites.

The malarial plasmodia are stained best by the Romanowski stain, which differentiates the nucleus.

The view that **mosquitos** were concerned in the distribution of malaria is very old, and has obtained in Italy since Roman times. *Koch* found it held as a popular belief also among negroes. In recent times *Manson* (1896) and *Bignami* (1896) were the first to turn their attention to the problem and to give hypotheses concerning the rôle played by mosquitos in the spread of malaria. *Bignami* carried out experiments along this line, but came to no positive result. *Ross* was the first (1897–98) to determine the cycle of development of the malarial plasmodium of birds (usually known as proteosoma). According to his investigations, the parasites taken up with the blood of the infected bird into the intestinal canal of mosquitos penetrate into the intestinal wall and there change into cysts in which innumerable rod-shaped germs develop. Becoming free, these germs gain entrance into the salivary glands of the mosquitos, and thence into the organism of the bird during the act of blood-sucking. Ross found the parasites in the blood of the infected bird in from five to nine days after the infection.

About the same time, *Grassi* found through painstaking observations that the distribution of malaria in man corresponded to the distribution of *Anopheles claviger* (*Fabricius*) (Fig. 542), and not to that of the common mosquito (*Culex pipiens*). Basing his experiments upon this observation, *Bignami* succeeded in producing malaria in healthy men by means of the bite of anopheles. Later *Grassi*, in coöperation with *Bastianelli* and *Bignami*, succeeded in determining the life-cycle of the malarial parasite It was then shown that several species of anopheles native in Italy (*Anopheles claviger* [*Fabricius*] or *Anopheles maculipennis* [*Meigen*], *Anopheles superpictus*, *pseudopictus*, *bifurcatus*) spread the malaria occurring in man, while *Culex pipiens* is the host of the parasites of bird-malaria

The **cycle of development of the malaria plasmodium** is as follows Within the blood (of man as well as of birds) the multiplication takes place first by *schizogony*. The young form of the plasmodia, represented by a small, unpigmented body, grows within the red cells (Fig 545, *1*) into a larger body (*5*), in whose central portion pigment

granules collect. This cell-body known as *schizont* shows in preparation for schizogony an increase of nuclei (*3*), and then divides into a number (varying with the species) of *spores* or *merozoites* (*4*) with the abandonment of a pigmented residual body. The merozoites then seek a red blood-cell (*1*), and the cycle is again begun.

In *sporogony* the merozoites develop into sexual individuals, macrogametes (*5*) and microgametocytes (*5a*). When taken up into the stomach by blood-sucking mosquitos, the sexual individuals become ripe for fertilization, the macrogamete by throwing off the karyosome (*6*), the microgametocyte through the formation of microgametes (*6a*). Copulation then follows (*7*). From the copula arises the motile oökinete (*8*), which in the wall of the mosquito's intestine becomes the oöcyst, in which through the division of the nucleus the sporoblasts (*9*) are formed, which in turn break up into a large number of sporozoites (*10*), which (*11*), becoming free, collect chiefly in the salivary glands, and are thence transferred by the bite of the mosquito to a new host, in whose blood they increase through schizogony (*1–4*).

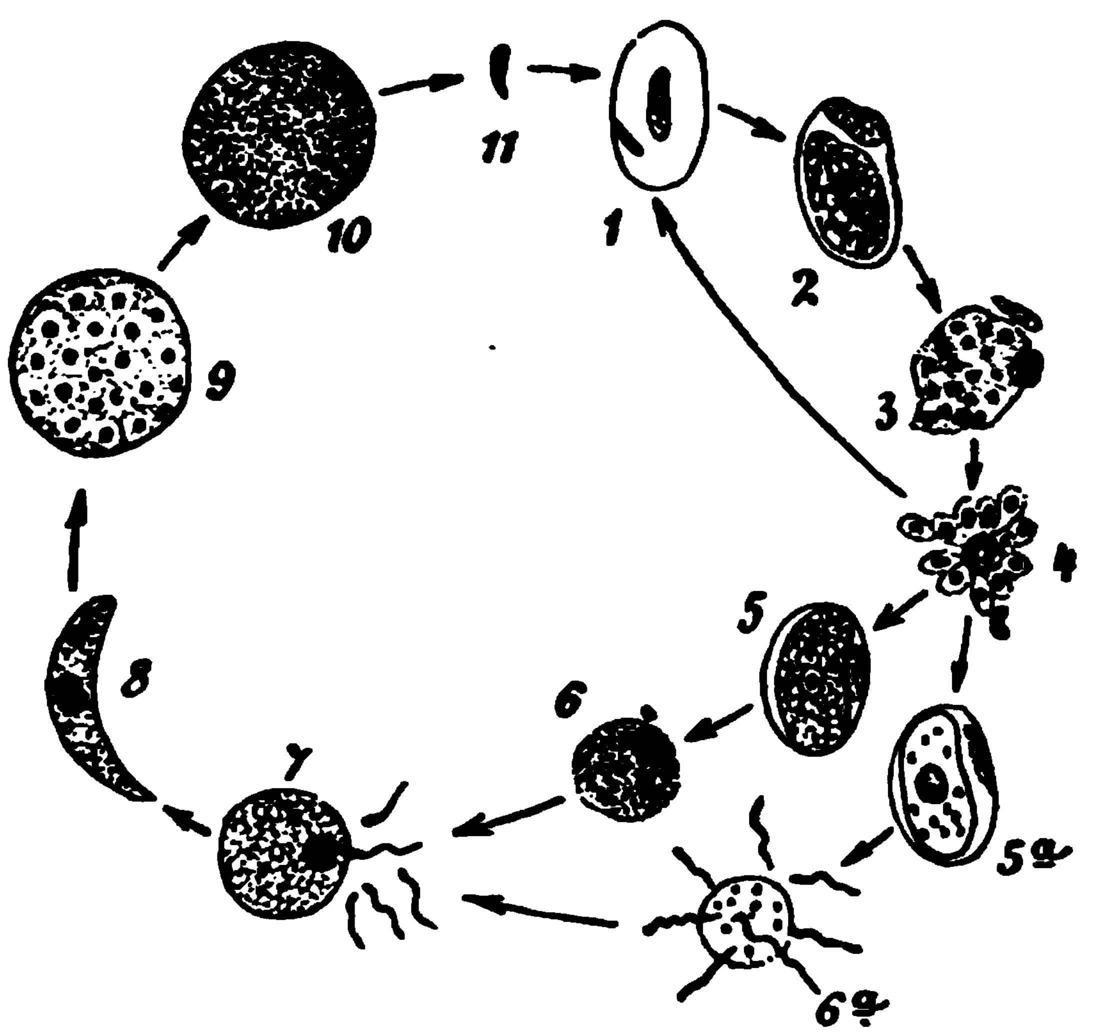

Fig. 545.—Cycle of development of *Proteosoma*. (After Schaudinn and Lühe.) *1*, Sporozoite (or merozoite) within a red blood-corpuscle; *2*, schizont; *3*, schizont with numerous nuclei; *4*, schizogony, formation of merozoites; *5*, macrogamete (female cell) arising from a merozoite; *6*, fully developed macrogamete after extrusion of the karyosome; *5a*, microgametocyte (male cell) arising from a merozoite; *6a*, microgametocyte surrounded by loosened microgametes (spermatozoa); *7*, fertilization of the macrogamete; *8*, oökinete; *9*, oöcysts with sporoblasts; *10*, oöcysts with sporozoites; *11*, free sporozoite.

According to the investigations of *Schaudinn*, the macrogametes and the microgametocytes of *Plasmodium vivax* may be distinguished from each other in the earliest stages of development within the red blood-cell, and also from the schizonts, at first through the peculiar structure of the nucleus and later through that of the protoplasm. In a new infection of tertian malaria the differentiation of the gametes began after the third attack. The growth takes place essentially slower than in the case of the schizonts. The pigment production is more abundant, while the nucleus is larger and less dense.

The larvæ of anopheles live chiefly in slowly flowing water. The eggs of *Anopheles claviger* require about thirty days at 20°–25° C. for the development of the insects, and these in turn lay eggs when twenty days old. The pupæ are resistant to drying, to cold, and to contamination of the water. The mosquitos fly during the evening and night, but do not rise very high above the level of the earth, and do not go very far away from the place of development. According to *Grassi*, *Bignami*, and *Bastianelli*, the æstivo-autumnal parasites will not develop in anopheles at a temperature of 14°–15° C., and grow only slowly at 20°–29° C.; at 30° C. they complete their entire development up to the formation of sporozoites in about seven days.

The literature concerning malarial parasites is extremely rich. The results of the latest investigations are given in the publications of *Grassi*, *Schaudinn*, *Mannaberg*, *Nuttall*, *Celli*, *Marchiafava*, *Bignami*, and *Lühe*.

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§ 189. Of the **ciliates** or **infusoria** occurring within the human organism the best known and most important is the **Balantidium** or **Paramæcium coli**, a unicellular animal 60–70 μ long, covered with short uniform cilia. At its anterior end it has a short peristoma (Fig. 546, *a*) which opens into a short gullet. The body is marked with parallel stripes and encloses a bean-shaped chief nucleus (*b*) and an accessory nucleus and two vacuoles. Multiplication takes place by division into two new individuals. It develops a permanent form in the shape of a spherical cyst with a firm membrane.

Balantidium coli occurs very often in the colon of swine without causing apparent changes. In cases of chronic diarrhœa in man it has been found in the dejections and in the colon, and probably stands in causal relation to the intestinal catarrh. According to investigations by Solowjew, Askanazy, Klimenko, and others the balantidia may penetrate into the mucosa and submucosa of the intestine and cause there ulcers. They may also wander into the blood-vessels.

FIG. 546.—*Balantidium (paramæcium) coli*, with two contractile vacuoles. (After Claus.) *a*, Mouth; *b*, nucleus; *c*, included starch grains; *d*, foreign body in the act of being extruded. High magnification.

Other species of **ciliates** have been observed in the intestine of man, *Balantidium minutum* (*Schaudinn*, 1899) and *Nyktotherus faba* (*Schaudinn*). In the paunch and reticulum of ruminants, in which the cellulose digestion is carried on, and in the blind intestine of horses, infusoria are universally present and occur in enormous numbers, for example, *Isotricha prostoma*. *Entodinium caudatum*, *Ophryoscolex caudatus*, and others.

(*Ciliates.*)

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II. Vermes (Worms).

A. Platyhelminthes (Flat-Worms.)

1. *Trematoda, Sucking* Worms.

§ 190. **The Trematodes** or *sucking-worms* are flat-worms of tongue or leaf shape. They possess a clinging apparatus in the form of ventral sucking-cups of varying number, and are sometimes furnished with hooks or clasp-like horny projections. The intestinal canal is without an anus, and is usually forked. The development takes place either by the direct growth to maturity of the embryos (*miracidium*) hatching from the eggs, or by the method of alternate generation through the *formation of germs within the host*. The miracidium, or ciliated embryo, penetrates into a snail or mussel, and there grows into a *germ-sac* (*sporocyst*), within which there later develops, either directly or after the formation of an intermediate generation of germ-sacs (*rediæ*), a swarming generation of *cercariæ*, which are provided with rudder-like tails. These lose their tails and penetrate into a new host (mollusks, arthropods, fish, amphibia), become encapsulated, and attain sexual maturity as soon as they reach the final host. The germ-sacs which produce cercariæ are designated primary germ-sacs ("*Ammen*"); if they first form rediæ and then cercariæ, they are called secondary germ-sacs ("*Grossammen*").

Distoma hepaticum, or liver-fluke, is a leaf-shaped sucking-worm about 28 mm. long and 12 mm. broad (Fig. 547). The cephalic end projects like a beak, and bears a small sucking-cup, in which the mouth is placed. Close behind this, on the ventral surface, is a second sucking-cup, and between the two lies the sexual orifice.

The uterus consists of a convoluted, globular sac behind the posterior sucking-cup. On each side of the hinder part of the body lie the yolk-sacs, and between the same are found the testicular canals, which branch many times. The forked intestinal tract (not visible in Fig. 547) is repeatedly branched.

The eggs (Fig. 548) are oval, 0.13 mm. long and 0.08 mm. broad. In water there develops an embryo, the *miracidium* (Fig. 549, *A*), with

cellular germ-balls (*a*); with the aid of its ciliated covering the embryo swims about, and seeks out a new host from the family of mollusks (*Limnæus minutus*). On penetration into the snail the cutaneous layer is thrown off, and the *miracidium*, which possesses an intestine, an excretion-organ and a brain-ganglion, becomes changed into a *sporocyst* (*B*), in which the intestine and nervous system atrophy, while the cellular germ-balls develop further (*B, a*) and form a *second generation of germ-sacs*, the *rediæ* (*B, b*). The rediæ (*C*), which possess an intestine (*C, a*), produce then within the same host the *cercariæ* (*D*) from cells which are loosened from their germ-matrix (*C, b*); these abandon the host and with the aid of a rudder-like tail swim about in the water. With the loss of their tails they become encysted upon almost any foreign body, and then reach their final host (usually through the food), in which they attain sexual maturity. The sexually mature animal inhabits the biliary passages; more rarely it is found in the intestine or inferior vena cava. The liver-fluke is rare in man, but common in cattle and sheep. The results of its invasion, especially when it is present in great numbers, are obstruction and ulcerative strictures of the bile-passages, formation of biliary concretions, inflammation of the tissues in the neighborhood of the bile-ducts, and hyperplasia of the periportal connective tissue of the liver with atrophy of the glandular tissue. The same changes are found in cattle. In sheep, following a marked invasion of the liver, there may develop a general cachexia.

FIG. 547. FIG. 548.

FIG. 547.—*Distoma hepaticum* with male and female sexual apparatus. (After Leuckart.) × 3.2.

FIG. 548.—Eggs of Distoma hepaticum. (After Leuckart.) × 200.

Distoma lanceolatum is only 8–9 mm. long and 2–2.5 mm. broad, is lancet-shaped, and the cephalic portion is not especially marked off from the body (Fig. 550).

The skin of the body is smooth. Two irregularly lobed testicles (*h*) lie close behind the ventral sucking-cup, in front of the ovary (*o*) and the uterus (*u*), the coils of which shine through the transparent body. The anterior coils are black with the ripe eggs, the others are rusty red. The yellowish-white yolk-sacs (*d*) lie in the middle of the lateral margin.

The oval eggs are 0.04 mm. long, and while still in the uterus contain an embryo which escapes only after several weeks following the casting-off of the eggs. Its metamorphoses are unknown.

Distoma lanceolatum likewise inhabits the bile-passages, but is very

rare in man. It is of more frequent occurrence in sheep and cats. When present only in small numbers, it causes no marked changes. In the presence of large numbers may excite inflammation and proliferation of the periportal connective tissue.

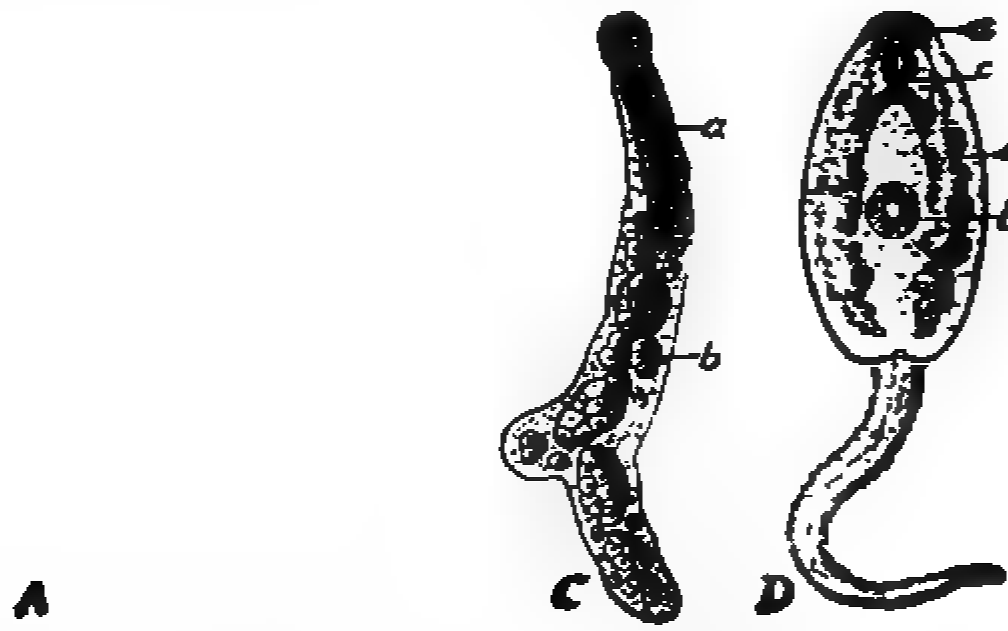

FIG. 550. Development of the liver-fluke. (After Leuckart.) *A*, Miracidium with germ-balls (*a*); *B*, sporocyst with germ-balls (*a*) and rediae (*b*); *C*, redia, with intestine (*a*) and germ-balls (*b*); *D*, cercaria with mouth (*a*), abdominal sucking-cup (*b*), intestine (*c*), and glands (*d*).

Distoma spathulatum (Fig. 551) is a sucking-worm occurring in man in Japan and China. It is 10–14 mm. long and 2.5–4 mm. broad. The eggs are 0.027–0.03 mm. long and 0.015–0.0[illegible] mm. broad. The parasite inhabits usually the bile-passages and the gall-bladder, but may also gain access to the pancreatic duct (Katsurada), and pass out into the intestine. When occurring in great numbers (Katsurada counted 4,361 in one case) it causes an obstruction to the outflow of the bile, and often excites a more or less severe inflammation and proliferation of connective tissue.

The parasite is found also in cats and dogs (Katsurada).

Distoma Westermanni (Kerbert), or *Distoma pulmonale* (Baelz) also occurs in Japan, China, and Corea. The worm is 7.5–10 mm. long, 5–7.5 mm. broad, egg-shaped, with slightly flattened ventral surface. The oval eggs are 0.09 mm. long and [illegible] mm. broad. The internal organization (Fig. 552) resembles that of the other trematodes. It occurs in man as well as in cats and dogs (Katsurada). It is found most frequently in the lungs, but occurs also in other organs: the pleura, brain, [illegible] intestinal wall, peritoneum, orbital cavity, [illegible] scrotum, etc. In each case it occupies small cavities surrounded by newly formed connective tissue, and occurs occasionally in pairs. In the lung it may be found also in the bronchi, the [illegible] which show inflammatory changes (Katsurada). [illegible] presence in the lung may give rise to hemorrhage and cause death. The number of lung-

flukes may run from twenty to thirty or even higher. Healing of the disease is possible after death of the parasite.

Distoma felineum (Rivolta) or *Distoma sibiricum* (Winogradow) is a flat, almost transparent sucking-worm, of from 8–10 mm. in length and 1.5–2.5 mm. broad, which is present in the bile-passages of the cat and dog, and in a few countries (Siberia) has been observed in man. According to Winogradow it is the most common parasite in Tomsk. Askanazy recently observed several cases in Königsberg. The sources of the infection were fish eaten raw (roach, *Lenciscus rutilus*).

The inflammatory proliferations which the different forms of distoma cause in the liver of man, as well as in animals, may be followed by the development of carcinoma.

In **Distoma hæmatobium** or *Bilharzia hæmatobia* (Fig. 553) the two sexes are separate. The mouth and ventral cups lie very close together on the tapering anterior extremity. In both sexes the sexual openings lie close behind the ventral sucking-cup. The male is 13–14 mm. long.

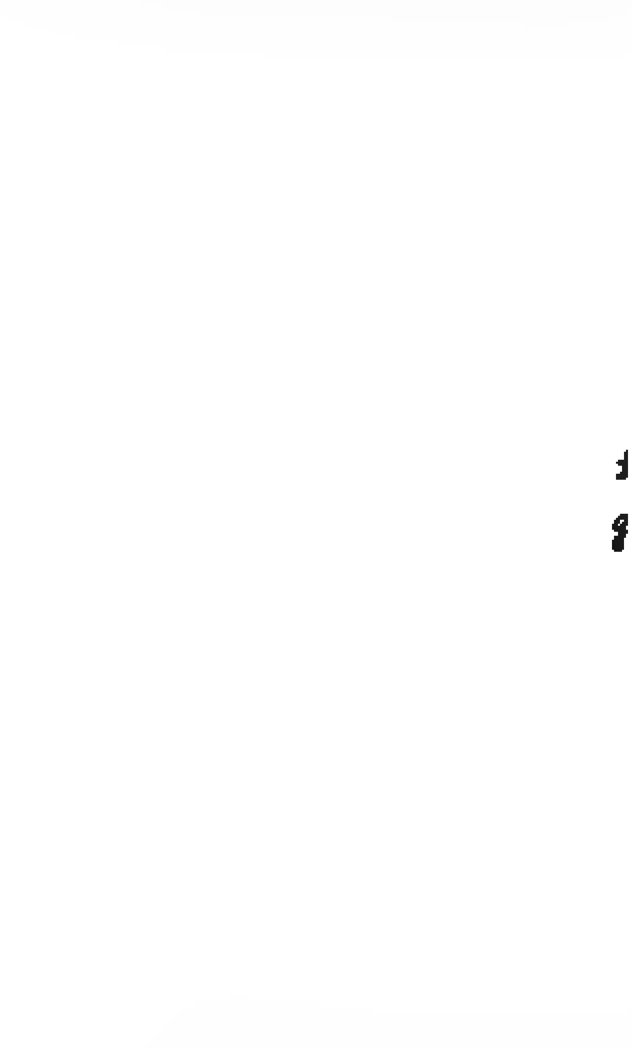

FIG. 551.

FIG. 552.

FIG. 551.—*Distoma spathulatum*. (After Katsurada.) *a*, Mouth sucking-cup; *b*, intestine; *c*, uterus; *d*, testicles; *e*, yolk-stalks; *f*, sperm-pouch; *g*, ovarium. × 6.

FIG. 552.—*Distoma Westermanni*, flattened by pressure, in the ventral position. (After Katsurada.) a, a_1, Mouth and abdominal sucking-cup respectively; *b*, intestinal loops; *c*, testicles; *d*, ovarium; *e*, yolk-stalks; *f*, shell-gland; *g*, uterus; *h*, excretory vessel. × 7.2.

The body is flat, but in its posterior portion is rolled together to form a tube (Fig. 553) which serves for the reception of the female.

The female is 16–19 mm. long and nearly cylindrical. The eggs are an elongated oval (Fig. 554), 0.12 mm. long, and possess a terminal or a lateral spine. According to observations by Sonsino, no alternation of generations occurs in the development of *Distoma hæmatobium*. The

part of intermediate host is taken by small crustacea, into which the ciliated embryo, swimming around in water, bores its way to become encapsulated in the tissues of its host. It is therefore probable that the infection may be transmitted through the drinking of water infected with the larvæ.

The worms are found in the trunk and branches of the portal vein, in the splenic vein, mesenteric veins, as well as in the vessels of the rectum and bladder; and may pass through the inferior mesenteric vein into the hæmorrhoidal and vesical veins, the veins of the ureter and prostate, and by chance into the inferior vena cava, and thence into the lungs. Their eggs are distributed therefore especially throughout the mucosa and submucosa of the ureters, bladder, and rectum, and occasionally also in the liver, lungs, kidneys, and prostate. While still within the urinary passages the cylindrical embryos (miracidia) covered with fine cilia may

FIG. 553.

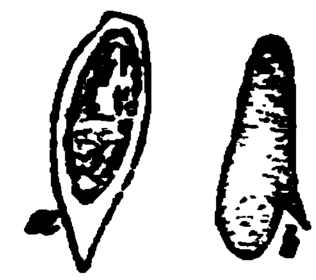

FIG. 554.

FIG. 553.—*Distoma hæmatobium.* (After Leuckart.) Male and female, the latter lying in the canalis gynæcophorus of the former. × 10.

FIG. 554.—Eggs of *Distoma hæmatobium.* (After Leuckart.) *a*, Egg with terminal spine; *b*, egg with lateral spine. × [illegible].

develop. Kartulis found them also in the skin of the leg and foot, and is of the opinion that the infection may take place not only through the intestine, but also through the skin.

The deposit of eggs causes severe inflammations which lead in part to tissue-destruction and in part to proliferations of the tissue, which appear in the mucous membranes as papillary and polypoid formations. In the bladder it may lead to incrustations and formation of concretions, and also to the development of fistulous tracts. In the liver the process leads to a connective-tissue induration. Following the inflammatory process, a development of carcinoma may take place in the bladder, seminal vesicles, prostate, and in the skin (Kartulis).

The parasite is found along the entire eastern coast of Africa, and also in Zanzibar, Tunis, Lake Nyassa, in Beyrout, and in Sicily. It is most common in Egypt, where about twenty-five per cent. of the native population suffer from the disease.

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2. *Cestoda (Tapeworms).*

§ 191. The **tapeworms** are *flat-worms devoid of mouth* or *intestine*, which increase after the method of alternate generation through the germination of a pear-shaped primary head or scolex, and remain united to the latter for a long time as a (usually) long, band-shaped colony. The single segments of this colony, the sexually active individuals, or **proglottides**, increase in size the more widely they become separated from their place of origin by the formation of new members, but outside of this are devoid of any outward distinguishing peculiarity. The pear-shaped **head** or **scolex**, on the other hand, is provided with from two to four suckers, and usually also with curved claw-like hooks. With the aid of these clinging organs the tapeworms fasten themselves to the intestinal wall of their host, which appears to be invariably one of the vertebrate animals. The scolices develop from a round embryo having four to six hooks, and are found as the so-called "measles" in the most diverse organs, chiefly the parenchymatous ones, from which they later pass by a passive migration into the intestine of their future host.

The *tapeworms occurring as parasites in man* belong to different families the *Tæniadæ* and the *Bothriocephalidæ*. The first occur in man either as "measles" or as tapeworms, the latter only as tapeworms.

§ [illegible]. **Taenia solium** in the fully developed condition possesses a length of [illegible] metres. The head (Fig. [illegible]) is of the size of a small pin's head, [illegible] with rather prominent sucking-cups. The crown of the head is not infrequently pigmented and bears a fairly large rostellum with about twenty-six plump coarse hooklets having short root processes. Following the head there is a thread-like neck of about an inch in length. At a certain distance from the head segmentation begins, the first segments being very short, but their length increases with their distance from the head (Fig. [illegible]); they become quadratic and finally longer than broad. The mature segments appear about 130 cm. behind the

Fig. [illegible]

Fig. [illegible]

Fig. [illegible]

Fig. [illegible]. Head of Taenia solium with projecting rostellum [illegible]

Fig. [illegible]. Half-grown and fully mature segments. Natural size. (After Leuckart.)

Fig. [illegible]. Two segments [illegible] (After Leuckart.) [illegible]

head, although the sexual organs are fully developed in earlier segments. The ripe segments (Fig. [illegible]) are, when stretched out, 9–10 mm. long and [illegible] mm. broad, and have rounded corners. The sexual opening is situated laterally just behind the middle of the segment. The uterus, which is filled with eggs, possesses seven to ten lateral branches which are separated from each other by a wide interval and break up into a varying number of [illegible] branching like a tree.

The parenchyma of the body of mature as well as of immature proglottides, or tapeworm segments (Fig. [illegible]), is divided into two chief layers, the central one being designated the middle layer, the peripheral one as the cortical layer. The middle layer contains the sexual apparatus (Fig. [illegible]), as well as the water vascular system ([illegible]) or excretory apparatus which traverses the whole tapeworm from the head to the last segment in the form of two canals lying in the lateral border of the middle layer. The canals are connected with each other at the posterior end of each segment ([illegible]) and also send out numerous fine, [illegible] branches into the body parenchyma.

The *sexual apparatus* consists of male and female sexual organs, which lie close together. A number of small, clear vesicles serve as testicles (*c*), they lie chiefly in the anterior portion of the middle layer The vas leferens (*e*), which is connected with the testicles by the seminal ducts (*d*), empies into a grooved papilla ituated on the lateral border *h*). The coiled end (*f*, *g*) ies in a muscular bag and nay be protruded through he sexual opening (*cirrus*). The female sexual opening ies close behind the male rifice in the same sexual loaca. The vagina (*i*) leads hence to the posterior border f the segment. Before this s reached it widens into the eminal vesicle, and behind his into the fructifying canl and the so-called "globular body." The germ-preparing organs, which must be sought in the immature segments, consist of a double ovary *k*) and a single albumin-gland (*l*); these are sac-like or tubular organs ying in the posterior portion of the segment and communicating with the lobular body. The latter is joined to the anteriorly located uterus (*n*), hich at the time of sexual maturity forms a straight canal. When the ggs enter the uterus from the globular body, in which they pass their rst stage of development, the above-mentioned lateral branches sprout ut and become filled with eggs. During this process the remaining sexal organs disappear.

FIG. 558.—Segment of *Tænia solium* with fully developed sexual apparatus. (After Sommer.) *A*, Surface view of segment; *B*, border of next anterior segment; *C*, that of next posterior segment; *a*, longitudinal excretory trunk; a_1, transverse anastomosis; *b*, longitudinal plasma-vessel; *c*, testicular vesicles; *d*, seminal ducts; *e*, vas deferens; *f*, cirrus-bag with cirrus; *g*, porus genitalis; *h*, border papilla; *i*, vagina; *k*, ovarium; *l*, albumin-gland; *m*, shell-gland, and oviduct in front of same; *n*, uterus.

The *cortical layer of the proglottides* is essentially muscular in nature, ut in addition contains a larger or smaller number of so-called calcareous odies, which are not entirely wanting in the middle layer as well. The usculature consists of smooth fibres, which form special groups in the ckers of the head. The surface of the tapeworm is covered with a clear cuticle, which forms the hooks on the heads.

b

FIG. 559.

FIG. 560.

FIG. 559.—Eggs of *Tænia solium*. *b*, With prime vitelline membrane; *a*, without primitive vitele membrane. (After Leuckart.) × 300.

FIG. 560.—Cysticercus cellulosæ, with fully developed head *in situ*. (After Leuckart.) × 4.

The *eggs in the ovary* are thin-skinned, pale and yellow, nearly globular cells. In the uterus they change into yellow balls having a thick, more or less opaque shell, covered with closely set spicules (Fig. 559, *a*). The latter is often surrounded by a second layer, an albuminous envelope (*b*) limited by a membrane; and in it there are embedded granules (primitive vitelline membrane). The diamer of the eggs, not including the vitelline membrane, is about 0.03 mm.

The thick-shelled spheres are not undeveloped eggs, but contain an nbryo with six hooklets. An intra-uterine development of the emyo therefore takes place, the ripe segments are pregnant animals.

The *further development of the embryos* enclosed in the brownish shells takes place ordinarily in a new host. Should they gain access to the stomach of a *hog*, the egg-shell is dissolved, and the embryos, thus set free, penetrate into the stomach or intestinal wall. Thence they pass either by the blood-stream or by an active migration through the tissues into this or that organ. Having reached a resting-place, the embryos undergo various metamorphoses and become changed inside of two or three months into a *cyst* filled with serum (Fig. 560), the inner wall of which shoots forth into a bud from which there develops a new tapeworm head, a *scolex*, as well as a sac enclosing the same, a *receptaculum scolicis*.

The cyst containing a tapeworm head is known as a "**measle**" or **cysticercus cellulosæ.** The scolices, when fully developed, possess a circle of hooklets, suckers, a water-vascular system and numerous calcareous bodies in their body-parenchyma. If they gain access to the human stomach, the cyst is dissolved, and there develops, through the formation of segments from the scolex (*Amme*), a new chain of proglottides, a new *Tænia solium*.

Fig. 561.—Cysticerci of the *Tænia solium*, in the epicardium and myocardium of a hog.

The *Tænia solium inhabits the small intestine of man*, and is acquired by the eating of uncooked pork, since the "measles" belonging to this parasite occur almost solely in the hog and in man. By means of its sucking-cups and its circlet of hooks it clings firmly to the mucosa of the intestine; the remaining portions float freely in the intestine. Usually but a single parasite is present in the intestine, although the presence of several at the same time is not rare. Occasionally as many as thirty or forty have been observed in one individual. They excite irritation of the intestinal mucosa, colic, and reflex disturbances of the central nervous system.

The "measles" occur in the tissues of the hog, sometimes singly, sometimes in great numbers (Fig. 561); and individual organs, as, for example, a muscle or the heart, may be thickly studded with them.

In man, *cysticerci* occur in the most varied tissues—the muscles, brain, eyes, skin, etc. In the meninges and in the brain the measle may appear in the form of mulberry or grape-like collection of cysts, known as *cysticercus racemosus* (Zenker). The cysts are for the greater part sterile, though some of them may contain a scolex.

The importance of the measle depends upon its location, but is in gen-

eral slight. Its presence in the brain often causes severe disturbances, but in other cases all signs of disease may be lacking. Locally it excites a slight inflammation, which leads to a thickening of the connective tissue in its immediate neighborhood. The cyst may retain its vitality for years. After the death of the scolex the cyst contracts and there is deposited within it a chalky mass. The hooklets are preserved in this mass for a very long time. Infection with the "measles" follows the introduction of eggs or proglottides into the stomach of man.

Tænia mediocanellata or **saginata** surpasses the *Tænia solium* not only in length, as it measures 4–7 metres and more, but also in its breadth and thickness, as well as in the size of the proglottides (Fig. 562).

The *head* is devoid of rostellum and circle of hooklets (Fig. 563), has a flat crown and four large, powerful suckers, which are usually surrounded by a black border of pigment.

The *eggs* resemble those of *Tænia solium*. The fully developed pregnant *uterus* (Fig. 564) has a large number of lateral branches which run close to each other, and instead of branching dendritically divide dichotomously. The sexual opening lies back of the middle of the lateral border. The segments discharged spontaneously are for the greater part empty of eggs.

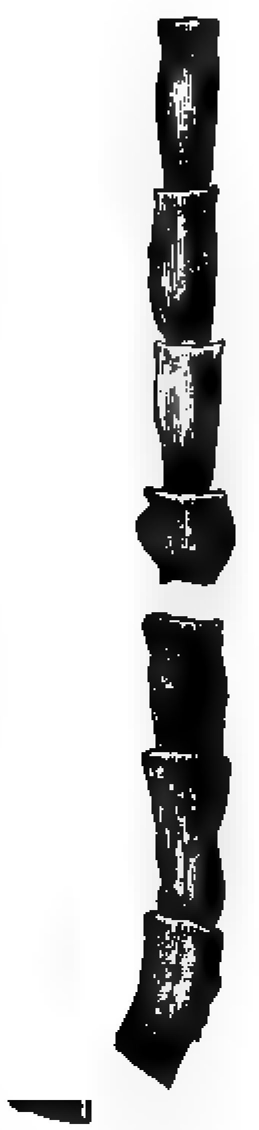

FIG. 562. FIG. 563. FIG. 564.

FIG. 562.—Portions of a *Tænia saginata*. (After Leuckart.) Natural size.

FIG. 563.—Head of *Tænia saginata*, retracted. Black pigmentation in and between the suckers. Unstained glycerin preparation. × 30.

FIG. 564.—Segment of *Tænia saginata*. (After Leuckart.) × ½.

The "measles" are found usually in the muscles and the heart, more rarely in the other organs of *cattle* (*Cysticercus bovis*). They are somewhat smaller than the measles found in pork.

The *development* follows a course similar to that of *Tænia solium.* Malformations of this tapeworm are of very frequent occurrence.

The parasite is acquired by man through the eating of raw beef. It has not been definitely settled whether the "measles" of this worm occur in man, but some authors (Arndt, Heller) believe that such an occurrence does take place.

By means of its powerful suckers the parasite is able to cling very firmly to the intestinal wall. Stieda has observed a case in which a tænia 15 cm. long had penetrated through the wall of the duodenum into the pancreas, and had caused tissue-necrosis and hæmorrhage in its neighborhood.

Tænia cucumerina or **elliptica** is 15–20 cm. long, and possesses a head with rostellum and circle of booklets. It is of very frequent occurrence in *dogs and cats,* but is rare in man. Its cysticercoid inhabits the louse and flea of the dog, more rarely the flea of human beings (*Grassi*).

Tænia nana, a small tapeworm of from 8 to 15 mm. in length, has a head with four suckers and a circle of booklets. It has been observed chiefly in Egypt and in Italy. *R. Grassi* was able to obtain several thousands of specimens from two Sicilians who had suffered from severe nervous disturbances. According to his investigations, the tænia passes its entire development, from the embryo on, within the same host. *Visconti* (Rendiconti R. Istituto Lombardo, xviii., 1886) found, at the autopsy of a young man from northern Italy, great numbers of *Tænia nana* in the lower portion of the ileum. In Germany it has been observed in only a few cases (*Mertens, Leichtenstern, Bilz*).

Tænia diminuta (*Rud.*) or *flavopuncta* (*Weinland*), *minima* (*Grassi*) is a tapeworm, 20–60 mm. long, and has a head without booklets. It is of common occurrence in rats and mice, and has also been observed in a few cases in man. According to *Grassi* and *Rovelli*, the measles live in a small butterfly, as well as in beetles.

Von Linstow has recently described as **Tænia africana** a large tapeworm with scolex devoid of booklets, which he observed among the negroes of German East Africa.

Besides those which also occur in man, tæniæ are of frequent occurrence in the **domestic animals,** both in the carnivora and in birds, as well as in the herbivora.

Tænia marginata of the dog is a tapeworm, 1–5 m. long, provided with a double circle of booklets. Its cysticercus forms cysts (*cysticercus tenuicollis*) of varying size in and under the serous membranes of sheep, cattle, goats, and hogs.

Tænia serrata is a tænia found in the dog. It is 50–100 cm. long, and possesses a circle of booklets. The cysticerci (*cysticercus pisiformis*) are found in rabbits and hares.

Tænia cœnurus is a tapeworm of the dog, 40–100 cm. long, and is provided with booklets. It passes its cystic stage most frequently in sheep, where it seeks the central nervous system and forms cysts varying in size from that of a millet seed to that of a hen's egg, which contain great numbers of scolices. Its presence in the brain [illegible] gives rise to the so-called "staggers" of sheep.

Tænia plicata [illegible] cm. long, *Tænia mammillana* 1–3 cm. long), and *Tænia perfoliata* 3–5 cm. long) occur in horses. *Tænia expansa* 4–5 m. long) and *Tænia denticulata* 25–80 cm. long) are the common tapeworms of cattle. Further, still other forms of tæniæ occur [illegible] as parasites in sheep and cattle.

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§ 193. The **Tænia echinococcus** lives in the intestinal canal of the dog. It is 4–5 mm. long and possesses only four segments, the most posterior of these surpassing in length all the rest put together (Fig. 565).

The small hooklets have coarse root processes and are implanted upon a rather bulging rostellum. Their number runs from about thirty to fifty.

The **cyst-worm** (**hydatid**) alone is found in man. It results from the introduction of tænia eggs into the intestinal canal.

If the embryo wanders from the intestinal canal into any organ, it changes into a *cyst*, which is not capable of active motion. It consists of an outer *lamellated*, very elastic *cuticle* (Fig. 566, *a*) and a parenchymatous layer (*b*) lying internal to this, consisting of granular masses and cells, and containing muscle-fibres and a vascular system. When the cyst has reached about the size of a walnut (sometimes earlier), there are formed from the parenchymatous layer small *brood-capsules* (*c*) which

produce a great number of *scolices*. The first stage of these tapeworm heads consists of coarsely granular protoplasmic masses (*d*) lying in the wall of the brood-capsule; these develop further and show cavities (*e*) communicating with the cavity of the brood-capsule, and later become differentiated into a tapeworm head (*f*) furnished with a circle of booklets. The head (*h*) which now protrudes into the lumen of the brood-capsule (*g*, *h*) is about 0.3 mm. long, possesses a rostellum with small, plump booklets, four suckers, a water-vascular system, and numerous chalky bodies in its parenchyma. Frequently the anterior part of the body is telescoped into the posterior part (*g*).

Fig. 568.—Full-grown Tænia echinococcus. (After Leuckart.) 12

In many cases the echinococcus cyst remains single. Its only change consists in an enlargement to the size of an orange or fist, through the formation of new brood-capsules and heads. The surrounding tissue forms a connective-tissue capsule, in which the cuticular cyst lies. The cavity of the cyst is filled with a clear fluid, which does not coagulate through boiling or on the addition of acids, and contains none or but little albumen, but on the other hand does contain sodium chloride, calcium oxalate, triple phosphates, uric acid, sugar (in the liver), and often also cholesterin. The brood-capsules are always situated on the inner surface, in case they are not mechanically dislodged; and are visible through the transparent parenchyma as small white points. Occasionally the cyst remains sterile.

In many cases daughter-cysts (Fig. 567, *c*) are formed. Their development proceeds in the depth of the cuticle independently of the real parenchymatous layer. Between two lamellæ of the cuticle there arises

Fig. 567.—[illegible] containing brood-capsules and scolices (schematic, [illegible]). *a*, [illegible] with vacuolar cells; *c*, brood-capsules; *d*, *e*, *f*, *g*, *h*, [illegible]

a nucleus or a number of nuclei, which surround themselves with a cuticle, and thereby become the center of a new set of layers. As the number of layers increases, the cavity grows larger and the contents become clear.

If the daughter-cysts grow they bulge out the wall of the mother-cyst like a hernial sac, until it finally gives way and liberates its contents. If they now pass outward by the side of the parent-cyst, they obtain from

FIG. 567.—*Echinococcus hydatidosus.* *a*, Surface of liver; *b*, indurated connective tissue; *c*, daughter-cysts within a parent-cyst, which has been opened by an incision; *d*, adhesions. Three-fifths natural size.

the parenchyma in which they lie an external capsule of connective tissue, and then produce brood capsules in the same manner as the primary cysts arising from the six-hooked embryos.

An echinococcus with an *exogenous proliferation* is called **echinococcus granulosus** (*scoleciparieus* Küchenmeister), or sometimes also **echinococcus veterinorum** from the fact that it is of frequent occurrence among the domestic animals.

A second compound form of the echinococcus is the **echinococcus hydatidosus.** It is characterized by the presence of inner *daughter-cysts* (Fig. 567, *c*). According to statements made by Naunyn, and also confirmed by Leuckart, the scolices and brood-capsules undergo a cystic metamorphosis, and so become changed into daughter-cysts which occasionally produce grand-daughter cysts. Through the formation of numerous daughter-cysts the chief cyst may attain a very large size.

The *infection of man* follows the ingestion of the eggs of the tænia which occurs in dogs. The cysts are most often found in the liver, but the echinococcus occasionally occurs in the most diverse organs—for example, in the lungs, spleen, kidneys, intestine, in a bone or in the heart. With the exception of the disturbance of the tissues from pressure and of the local inflammation which it causes (the latter leading to the formation of a connective-tissue capsule in many organs) the cyst often

produces no harmful effects upon the affected individual. It often dies on attaining a certain size (that of a walnut to that of an apple), the fluid is absorbed, the cyst contracts, and there remains within it a fatty, cheesy detritus, which often calcifies to a mortar-like mass. The hooklets are preserved for a very long time.

In other cases the echinococcus becomes larger, particularly when endogenous or exogenous daughter-cysts develop. It may become dangerous through its size alone. Severe inflammations are occasionally produced, particularly after trauma or after rupture of the cyst into one of the body-cavities. Rupture into a blood-vessel may also occur and lead to the metastasis of cysts and an embolic blocking of vessels. In more favorable cases rupture may take place externally or into the intestines.

The spontaneous spread of brood-capsules and scolices in the same

Fig. 568.—Transverse section of an *Echinococcus multilocularis*. *a*, Alveolar echinococcus tissue; *b*, liver tissue; *c*, cavity produced by softening; *d*, fresh nodules. Natural size.

host, as well as the experimental transplantation of the same into another host (Alexinsky, Dévé) may lead to the formation of new cysts.

The form of the parasite known as **echinococcus alveolaris** or **multilocularis** presents itself as a hard tumor, situated usually in the liver, rarely in other organs (brain, spleen, adrenal), and possesses an alveolar structure (Fig. 568), in that a firm, dense connective-tissue mass encloses numerous cavities. Its contents are translucent and gelatinous, or consist of fluid and a gelatinous substance. The cavities are in part spherical and in part irregular in shape. Usually, through the softening and disintegration of the parenchyma, ulcerative cavities (*c*) are formed. In other places the tissue is fibrocaseous, necrotic or calcified, or is impregnated with bile. At times the caseation of the proliferating tissue is the most prominent feature of the process: at other times the alveolar structure. When the development of the colonies has progressed further, there appear in the tissue gray and yellowish nodules (*d*) in which cavities containing colloid plugs (chitin-cysts and coils) are developed.

The exquisite alveolar structure has given rise to the theory that this form of echinococcus is an alveolar, colloid-containing tumor of the liver. Virchow first recognized the true nature of the condition, and demonstrated that the so-called colloid masses were echinococcus cysts.

According to the investigations of Melnikow-Raswedenkow the alveolar echinococcus is to be regarded as a different species, which increases in the tissue of the host in a peculiar manner, suggesting the mode of development of the Trematodes; and in many cases spreads by both hæmatogenous and lymphogenous metastases from the primary focus of development to other organs (lymph-glands, lungs, brain).

Should the alveolar echinococcus occurring in any organ, as, for example, in the liver, encroach upon the neighboring tissues, there are found in the latter finely granular multinucleated protoplasmic structures surrounded by granulation tissue. Later small chitinous cysts develop or a folded membrane studded with granular masses, while the granulation tissue becomes changed into fibrous connective tissue. The majority of the cysts remain sterile. Scolices develop only in a few. Ovoid granular structures with a thin membrane may be formed and are regarded by Melnikow as embryos. The chitinous membranes which lie in the granulation tissue are often surrounded by giant-cells.

The life-history of the alveolar echinococcus outside of the parenchyma of the organ is unknown; the feeding to dogs has given no positive results. It appears that the embryos and scolices of the same are not capable of development in the intestine of the dog.

The ordinary echinococcus is widely distributed, though not very common. It is of most frequent occurrence in Iceland, where the inhabitants live in very close association with dogs. The alveolar echinococcus has been observed chiefly in Switzerland, South Germany, Austria, and in Russia.

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§ 194. **Bothriocephalus latus** (Bremser) or **pithead** is the most formidable tapeworm of man, measuring from 5–8 metres in length, and consisting of three thousand to four thousand short but broad segments (Fig. 569), which are broadest in the middle region and narrower again at the end. The length of the largest segment is about 3.5 mm., the breadth about 10–12 mm.

The head (Fig. 570) has a long oval or club shape, is about 2.5 mm. long and 1 mm. broad. It is somewhat flattened, and possesses on each lateral margin a slit-like depression, and is mounted upon a filiform neck.

FIG. 569. FIG. 570.

FIG. 569.—*Bothriocephalus latus.* (After Leuckart.) Natural size.

FIG. 570.—Head of *Bothriocephalus latus* of Bremser. (After Heller.) Enlarged.

The body is thin and flat like a ribbon, with the exception of the central parts of the segments which project somewhat outward. At this spot the uterus is found, in the shape of a single canal, which forms a number of coils (Fig. 571, *m*). When the eggs collect here in great numbers the lateral coils of the uterus arrange themselves in folds, so that a remarkable rosette-like appearance is produced. The sexual openings lie in the middle line of the ventral surface, near to the anterior border of the segment, the female orifice (*o*) being close behind the male opening (*f*).

The ovary (*g*) is a double organ which lies in the middle layer; the yolk-chambers (*h*), on the other hand, are located in the cortical layer. The shell-gland (*k*) lies behind the collecting-tube (*i*) of the yolk-chambers. The testicles consist of clear vesicles (*b*) which lie in the lateral portions of the middle layer, and communicate by means of fine canals (*c*) with the vas deferens (*d*), which terminates in the cirrus-sac (*e*, *f*).

The *eggs* (Fig. 572) are oval, and are about 0.07 mm. long and 0.045 mm. broad. They are surrounded by a thin, brown shell, the anterior pole of which forms a sharply outlined cap-like cover.

The *Bothriocephalus latus* occurs chiefly in Switzerland, in the north-eastern parts of Europe, in Holland and in Japan, and lives, as does the

FIG. 571.—Median portion of a proglottis of *Bothriocephalus latus*, seen from the dorsal surface. The cortical layer of the segment has been removed except a border on each side, and the middle layer thus exposed. (After Sommer.) *a*, Lateral vessels; *b*, testicular vesicles; *c*, testicular canaliculi; *d*, seminal ducts; *e*, posterior, *f*, anterior hollow-muscle apparatus (cirrus-sac of vas deferens); *g*, ovary; *h*, yolk-chambers lying in the cortical area; *i*, collecting-duct of yolk-stalk, branches of which lead ventrally to the yolk-chambers; *k*, shell-gland; *l*, beginning of the uterus; *m*, loop of uterus filled with eggs, the orifice of uterus opening on the anterior surface; *n*, vagina; *o*, vaginal opening. × 25.

Tænia, in the small intestine of man. According to Bollinger it is rather frequent in Munich. The first stage of development of the eggs takes place in water. After the lapse of months there develops an embryo (*Oncosphæra*) armed with six hooklets and covered with ciliæ (Fig. 573). This develops, in some intermediate host as yet unknown, into a measle (*Plerocercoid*), which, according to the investigations of Braun in the Russian Baltic provinces, seeks out as second intermediate host the pike or tadpole, and develops in the muscle or internal organs of these animals into a sexless tapeworm. According to Grassi and Parona, the measle of Bothriocephalus latus in Italy occurs in the pike and in the river-perch. In Japan it is found most frequently in the *Onchorhynchus Perryi* (Ijima, Leuckart). Zschokke found it in the Lake of Geneva in the following forms of fish:

FIG. 572. FIG. 573.

FIG. 572.—Eggs of *Bothriocephalus latus*, the one at the right having been emptied of its yolk-contents. (After Leuckart.)

FIG. 573. Free embryo of *Bothriocephalus latus* with ciliated envelope. (After Leuckart.)

Lota vulgaris, Perca fluviatilis, Salmo umbla. Esox lucius, Trutta vulgaris, and *Trutta lacustris*. It is found most often in the tadpole (*Lota vulgaris*) and in the perch (*Perca fluviatilis*). Should the measle gain entrance, through the ingestion of the fish mentioned, into the intestinal canal of man, it again attains sexual maturity. According to Braun and Parona the measles may also be brought to development in both dogs and cats. The presence of Bothriocephalus in the intestine gives rise to a gradually increasing anæmia, which resembles pernicious anæmia. The diminution of the red blood-cells and of the hæmoglobin content of the blood is probably due to the fact that after the death of the tapeworm poisonous products arise having an injurious action upon the blood-corpuscles.

Bothriocephalus cordatus (Leuckart) is a tapeworm, of 80–115 cm. long, and has a heart-shaped head, whose sucking-grooves are flattened. The breadth of the ripe segments is about 7–8 mm.; the length, about 3–4 mm. In Greenland and Iceland it is a frequent parasite of the dog, seal, and walrus, and is found occasionally in man. The measles likewise occur in fishes.

Bothriocephalus Mansoni (*Cobbold*) or *liguloides* (Leuckart) is the measle (plerocercoid) of a tapeworm which has been observed a few times (Manson, Ijima, Murata) in the body-tissues and in the descending urinary passages or in the urine. Its origin is not known.

Bothriocephalus felis, which occurs in cats, is very similar to the Bothriocephalus latus.

Bothriocephalus latus occurs also in dogs. In the United States this worm is found occasionally in individuals who have come from the various infected regions of Europe. In the mining regions of Northern Michigan it has been found a number of times in Finns.

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B. Nemathelminthes (Round Worms).

§ 195. All the **round worms** which occur as parasites belong to the **Nematoda**. They possess a slender, cylindrical, elongated, at times filiform body without segments or appendages. The cuticle is thick and elastic. The mouth opening is found at one extremity, and is provided

sometimes with soft and sometimes with horn-like lips. The elongated intestine, together with the pharynx and chyle-stomach, extends through the entire body-cavity (Fig. 574) and opens upon the ventral surface a short distance from the (usually) awl-shaped posterior extremity. The sexual organs and their openings are also found on the ventral surface. The female sexual orifice is located at about the middle of the body, less frequently near the anterior or posterior extremity (Fig. 574, *A*, *a*). In the male the sexual opening and the anus are located together (*B*, *c*). The chitinous covering of the lower gut forms in the male the means of clinging during the act of copulation. The males are usually smaller than the females. The development is direct, and the metamorphoses are not striking. The nematodes occurring in man are in part harmless parasites of the intestine, and in part very dangerous, sometimes even fatal, parasites of various organs.

§ 196. **Ascaris lumbricoides,** the common round-worm (Fig. 574) is a light-brown or reddish, cylindrical worm with tapering ends. The female (*A*) is 25–40 cm. long, the male (*B*) is much smaller, and the posterior extremity of the latter is bent in the form of a hook and provided with two spicules (*c*) or chitin processes.

The mouth opening (*b*) is surrounded by three muscular lips bearing fine teeth. The female sexual opening (*A*, *a*) lies anterior to the middle of the body. The eggs which the mature female contains in enormous numbers possess in their fully developed condition a double shell (Fig. 575) and around this an albuminous envelope. They are about 50–70 μ in length. The worm inhabits the entire intestinal tract, but most frequently the small intestine. It is the most common parasite of man, and is found frequently in very great numbers. When mature females are present the fæces contain the eggs in great numbers. These are very resistant to external influences, for example, to drying and freezing.

FIG. 575.

.—*Ascaris lumbricoides.* (After Perls.) *A*, Female; *B*, male. Natural size. At *a* is the female sexual orifice; *c*, the two spicules of the male; *b*, the (enlarged) cephalic end with the three lips.

FIG. 575.—Egg of *Ascaris lumbricoides*, with shell and albuminous covering. (After Leuckart.) × 300.

The eggs require no intermediate host (Lutz, Leuckart, Grassi, Epstein). Man is infected by the ingestion of eggs which have been expelled from the bowel and have matured in the fæces. According to feeding-experiments which Epstein carried out on human beings with eggs which had been cultivated in damp fæces for a long time, the roundworm attains its maturity in from ten to twelve weeks after the ingestion of the eggs. At this time the male is 13–15 cm. long, and the female from 20–30 cm. Their presence in the intestine does not cause any noticeable disturbance. Only when present in large numbers do they sometimes, especially in children, cause intestinal catarrh, vomiting, nervous disturbances and convulsions. Occasionally the worm crawls into normal and pathological openings in the wall of the intestinal canal, and in this way causes trouble. Thus, when it crawls into the ductus choledochus, it may produce bile-stasis. If it penetrates through an ulcer into the peritoneal cavity or into a hernial sac, it may excite inflammation of the tissues concerned. According to Leuckart it may also penetrate the uninjured intestinal wall. It is very frequently passed with the stools *per anum*, but at times *per os* in vomiting. From the pharynx it may wander into the larynx.

In the **domestic animals** ascarides are of frequent occurrence. *Ascaris lumbricoides* is found in swine (*Ascaris suilla*) and in cattle (*Ascaris vituli*). *Ascaris megalocephala*, a round worm whose female is 18–37 cm. long, is a common parasite of the horse and donkey. *Ascaris mystax*, whose female reaches a length of 12 cm., is found frequently in dogs and cats, and has also been observed in man. Various species, designated as *Heterakis*, occur in birds. *Heterakis maculosa*, the round worm of pigeons, may cause the death of the pigeon when occurring in large numbers within its intestine.

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§ 197. **Oxyuris vermicularis**, *awl-tail*, *pinworm*, or *threadworm* is a small round worm (Fig. 576), the female being about 10 mm. long (*a*, *b*) and pointed at the caudal extremity like an awl, while the male is about 4 mm. long (*c*) with a blunt posterior end, the anus being provided with a spiculum.

The eggs (577, *a*), which the body of the female often contains in very great numbers, are 50 μ long and 24 μ broad, have a flat and a curved surface, and a shell which is covered by a thin albuminous layer. *Oxyuris vermicularis* inhabits the large intestine and the lower portion of the small intestine. According to Zenker and Heller only the impregnated mature females are found in the large intestine, the young individuals and the males remain in the small intestine. They occur very frequently in larger or smaller numbers. At night they often wander from the rectum over the anal region, and may enter the vagina; they excite

itching of the affected parts. In the pelvic peritoneum encapsulated worms or eggs have been observed a number of times. It has not yet been determined whether they can penetrate the intestinal wall (Vuillemin). Wagener found dead and calcified worms in the submucosa of the intestine.

For the development of the eggs (Fig. 577, *a–e*), it is necessary after their expulsion with the fæces that they again be taken into the stomach of man or beast. It is very probable that the original host may again infect himself with oxyuris, in that, for example, the eggs becoming attached to his finger during the act of scratching may later get into his mouth.

The eggs are very resistant to drying, and in this condition may be widely scattered.

FIG. 576. — *Oxyuris vermicularis.* *a*, Sexually mature female; *b*, female full of eggs; *c*, male. (After Heller.) × 10.

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§ 198. **Anchylostoma duodenale** (*Dochmius duodenalis*, or *Strongylus duodenalis*, or *Uncinaria duodenalis*, also *Uncinaria Americana* [*Stiles*]), Hook-worm, is a small worm belonging to the family of *Strongylides*, which inhabits the upper part of the small intestine (Fig. 578). The cylindrical body of the female is 5–18 mm. long, that of the male 6–10 mm. The cephalic end (Fig. 579) is curved toward the dorsal surface, and possesses a bellied mouth-capsule (*d*). It is almost completely divided dorsally, and the cleft is covered by two chitinous lamellæ. On the ventral border there are four incurving teeth (*b*), on the dorsal border two teeth which are perpendicularly placed (*c*), all being held together by chitinous bands.

The male is provided at its caudal extremity with a threefold bursa (Fig. 578, *i*) and two thin, fishbone-like spicules (*p*). In the female the posterior end is pointed, and bears an awl-shaped spine; the vulva lies posterior to the body centre. The oval eggs (Fig. 580) are 44–67 μ long, 23–40 μ broad. They undergo the first stages of cleavage in the human intestine (*a–d*), develop further in muddy water (*e, f*), and may then, if brought into the human intestinal tract, develop again into sexually mature animals. With its teeth the worm works its way into the

mucous membrane as far as the submucosa, and sucks itself full of blood. Its point of attack is distinguishable later by a small ecchymosis in the middle of which there is a white spot with a central perforation. Occasionally there are found in the intestinal mucosa small cavities filled with blood, within each of which there lies a coiled-up worm. The para-

FIG. 577.—Eggs of *Oxyuris vermicularis* in different stages of development. (After Zenker and Heller.) *a, b, c,* segmentation of yolk; *d,* tadpole-shaped embryo; *e,* worm-shaped embryo. × 250.

sites, when present in large numbers, cause a continuous and serious loss of blood, which may lead to the most severe forms of anæmia (***Egyptian chlorosis***), but they are not infrequently found in individuals who present no symptoms of disease. The parasite is very common in the tropics, and also in Japan. According to Griesinger and Bilharz about one-quarter of the native Egyptians suffer from this disease. The parasite was very often observed in the workmen engaged in the Saint Gotthard tunnel. According to Menche and Leichtenstern the brick-fields of the Rhine provinces are to a great extent infected with anchylostoma (brick-burner's anæmia).

In 1903 the worm was distributed to an extraordinary degree throughout the mines of the mining district of Dortmund, so that in the autumn of that year over seventeen hundred individuals infected with the worm were found.

The infection takes place chiefly through larvæ ingested with the drinking-water and food. According to the investigations of Looss and Schaudinn, the larvæ may penetrate through the skin into the veins, thence are carried into the lungs, whence they wander through the bronchi, trachea, and larynx into the intestinal tract. In experiments made upon apes the larvæ may be found in the intestine within twenty-four hours.

According to *Stiles* (1902), the hookworm disease of the American continent is due to a distinct species from that found in Europe. He distinguishes them as the Old-World hookworm and the New-World hookworm (*Necator americanus* or *Uncinaria americana*). The latter form is prevalent throughout the Southern United States as far north as the Potomac River, and in the West Indies, and has also been found in Italy, Africa, China, and the Philippines. It is a cylindrical worm 7–11 mm. long with a dorsal and ventral pair of lips, a prominent dorsomedian buccal tooth, and four buccal lancets. In the male the dorsal ray of the bursa divides at the base and each branch possesses two tips. In the female the vulva is in the anterior half of the body. The eggs have more sharply rounded poles than those of the Old-World worm. It is estimated that about ninety per cent of the rural population of Porto Rico is infected with this parasite, and in some parts of Florida a similar degree of infection is reported. According to *Stiles*, the piney-wood and sandy-soil portions of the South are especially regions of infection. In these regions "ground itch" is of common occurrence, and :-

believed now to be due to the penetration into the skin of the larvæ of the hookworm. Among the most striking symptoms of the American infection are anæmia, perverted

FIG. 579.

FIG. 580.

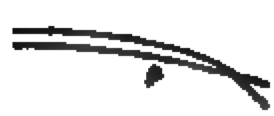

FIG. 578.

FIG. 578.—Male of *Anchylostoma duodenale*. (After Schulthess.) *a*, Head with mouth-capsule; *b*, œsophagus; *c*, intestine; *d*, anal-glands; *e*, cervical glands; *f*, skin; *g*, muscle-layer; *h*, porus excretorius; *i*, three-lobed bursa; *k*, ribs of the bursa; *l*, testicular canal; *m*, seminal vesicle; *n*, ejaculatory duct; *o*, groove of latter; *p*, penis; *q*, penis sheath. × 18.

FIG. 579.—Cephalic end of *Anchylostoma duodenale*. (After Schulthess.) *a*, Mouth-capsule; *b*, teeth of ventral border; *c*, teeth of dorsal border; *d*, mouth cavity; *e*, skin protuberance on ventral side of head; *f*, muscular layer; *g*, dorsal groove; *h*, œsophagus. × 100.

FIG. 580.—Eggs of *Anchylostoma duodenale*. (After Perroncito and Schulthess.) *a–d*, Different stages of segmentation; *e*, *f*, eggs with embryos. × 200.

appetite ("clay-eaters"), pain and tenderness in the epigastrium, delayed puberty, mental lassitude, etc. The "cotton-mill anæmia" of the South is due to a moderate degree of hookworm infection. The economic importance of uncinariasis in America

is very great. It is estimated that thirty per cent of all deaths in Porto Rico are the result of hookworm infection. According to *Stiles*, this infection is chiefly responsible for the inferior mental and physical condition of the poorer classes of whites in certain parts of the Southern States.

Eustrongylus gigas, a palisade-worm of red color, whose female reaches a length of 1 metre, is a very rare parasite, which has been observed only a few times in the kidney-pelvis of man. It occurs very frequently in dogs. It possesses a mouth-opening with six papillæ; the male has on its posterior extremity a bursa with a single spiculum. The eggs are oval, 0.06 mm. long, and provided with a rough albuminous capsule.

Strongylus longevaginatus, a thread-like, white worm, 26 mm. long, was once observed in the lung of a boy.

In the **domestic animals** *Strongylides* occur in much greater numbers than in man, and are in part inhabitants of the intestine, and in part of the lungs (*Müller*, "Die Nematoden der Säugethierlungen," *Deut. Zeitschr. f. Thiermed.*, xv., 1886).

Dochmius trigonocephalus and *Dochmius stenocephalus* occur in the intestine of dogs, and give rise to anæmia similar to that produced by the Anchylostoma in man.

Strongylus armatus is a common parasite of the horse, which enters the intestinal tract as an embryo, bores into the intestinal wall (*Olt*), thence into the liver, by way of the portal vein, and further into the lungs and the organs of the major circulation. Following this migration, it may develop in the most diverse organs and cause the formation of fibrous nodules, which become calcified after the death of the parasite enclosed in them. In the intestinal wall it may develop after direct migration or after embolic lodgment in the part, and leads to the formation of cavities, from which it again breaks through into the intestinal lumen. In the mesenteric arteries it attains sexual maturity, and causes thrombosis and the formation of aneurisms. The male of the mature worm is 20–30 mm. long; the female, 20–55 mm.

Strongylus tetracanthus, which inhabits the large intestine of the horse, causes a hæmorrhagic enteritis when present in large numbers.

Strongylus paradoxus is an extremely common parasite of the lungs of hogs. *Strongylus capillaris*, *Str. commutatus*, and *Str. filaria* are frequent parasites of the lungs of goats and sheep, and different species may be present in the same lung at one time (*Schlegel*, "Die durch Strong. capillaris verursachte Lungenwurmseuche der Ziege," *Arch. f. wiss. Thierheil.*, 25 Bd., 1899). The latter causes in sheep a bronchitis and nodular proliferating pulmonary inflammations; through the swallowing of many embryos inflammations of the intestine may also be produced.

Strongylus rufescens and *Str. paradoxus*, *Nematoidium ovis pulmonalis* (*Lydtin*), or *Pseudalius ovis pulmonalis* (*Koch*) are also inhabitants of the lungs of sheep, the last-named causing a pseudotuberculosis. *Str. commutatus* and *Str. pusillus* occur in the lungs of the hare and rabbit; *Str. syngamus* and *bronchialus* in the trachea of birds; and excite inflammations. *Str. micrurus* (*Strose*, "Bau von Strongylus micrurus," *Deut. Zeitschr. f. Thiermed.*, xviii., 1892) occurs in cows and calves, in arterial aneurisms as well as in the respiratory passages.

Strongylus pusillus causes in cats a pulmonary disease resembling tuberculosis (*Jeanmaire*, "Ueber die hist. Veränd. der Lunge bei der verminösen Pneumonie der Katze und des Hasen," Inaug.-Diss., Freiburg, 1900). *Syngamus trachealis* (*Klee*, "Der gepaarte Luftröhrenwurm des Geflügels," *Deut. Thierärztl. Wochenschr.*, 1899) is a dangerous parasite of birds, particularly of pheasants, in the trachea of which it appears in great numbers, and attaches itself to the mucous membrane. It is easily recognized by its red color. Similar to the last-named is *Syngamus bronchialis*, which has been observed a few times in geese and ducks.

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§ 199. **Anguillula intestinalis** (Fig. 581) is a worm of 2.25 mm. length, which is found in the intestine, particularly in the *tropics*, and in

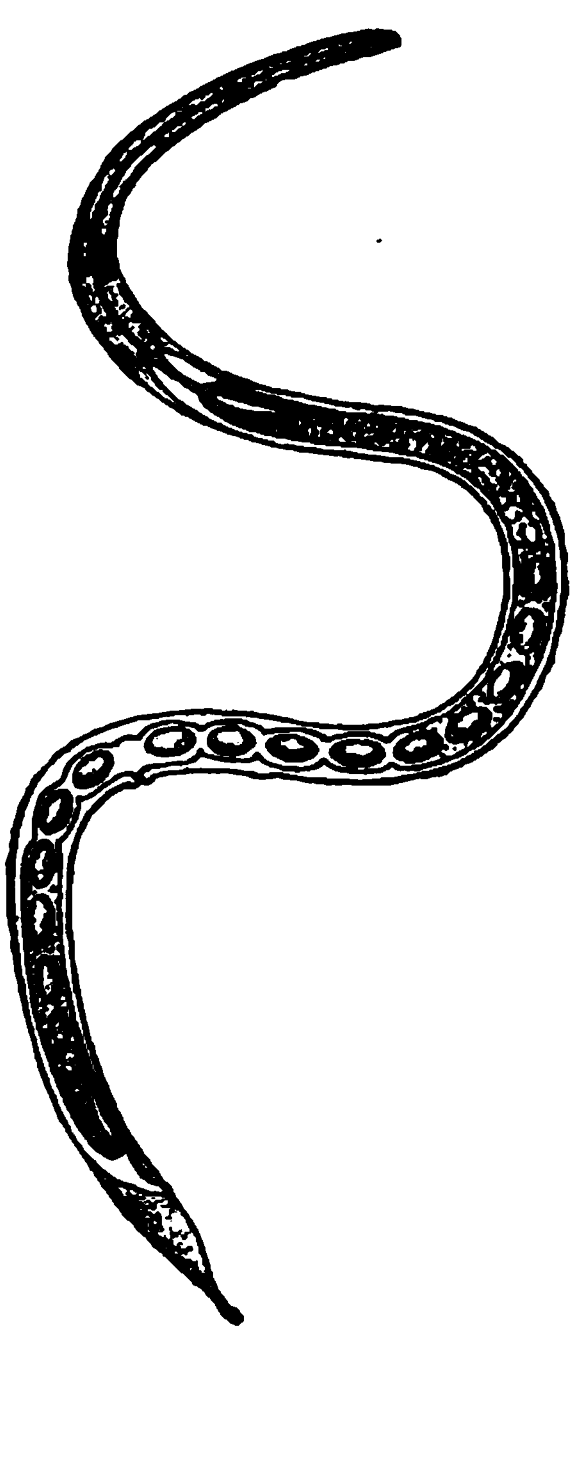

FIG. 581.—*Anguillula intestinalis*. (After Braun.)

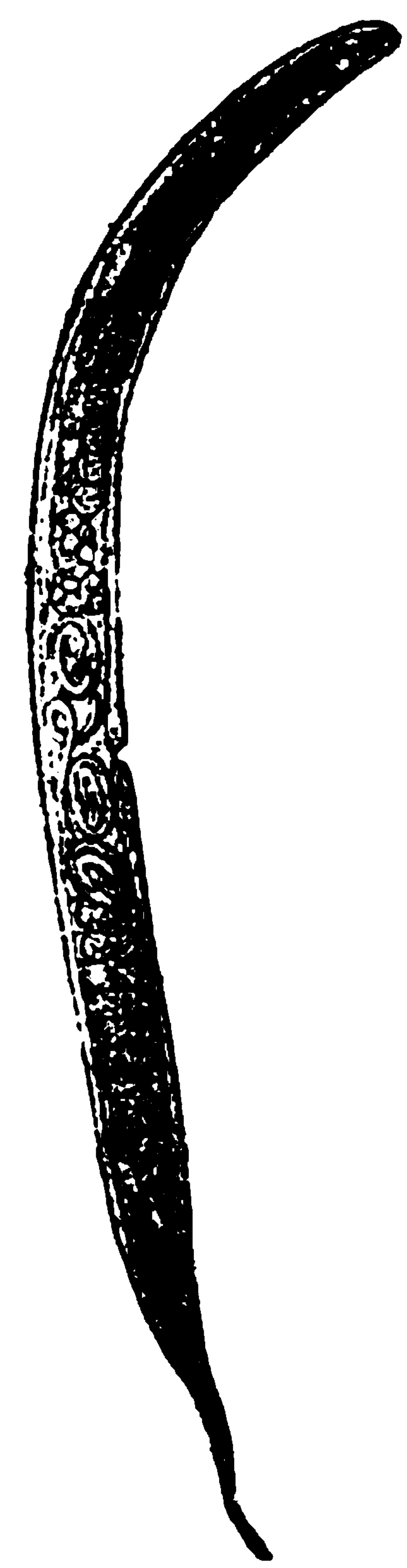

FIG. 582.—Female of *Anguillula stercoralis*, with eggs and embryos. (After Perroncito.) × 85.

Italy, and has been occasionally observed in Switzerland, Germany, Belgium, and Holland (probably transported from Italy), under similar conditions as the Anchylostoma duodenale. According to the observations

of Leuckart, Golgi, Grassi, Leichtenstern, Zinn and others, the *Anguillula intestinalis* is a hermaphrodite, the eggs of which develop even in the intestine to embryos of 0.2 mm. in length; and in the presence in the intestine of numerous parent-worms are found in the fæces in great numbers. In the stools they become changed within about twelve hours into filaria-like larvæ, which, when gaining entrance into the human intestine, again grow into parasitic anguillulæ, which are again able to produce eggs capable of development. In addition there also occurs a development with an intermediate sexual generation, a heterogony.

In the event of a sexual development the embryos grow outside of the body in about three days into sexually mature animals (female 1.2 mm. long, male 0.88 mm.) which are known as *Anguillula* or *Rhabditis stercoralis* (Fig. 582), and were formerly regarded as a separate species. The embryos of the separate sexual individuals develop into filaria-like larvæ, which, entering the intestine of man, again grow into parasitic anguillulæ.

According to Leichtenstern and Zinn the filaria-like larvæ of the direct development are more resistant than those of the sexual. The sexual mode of multiplication occurs particularly in the anguillula, coming from the tropics, while in the indigenous form (brick-laborers of Germany, Belgium, Holland) the direct metamorphosis predominates. Leichtenstern has explained this by the assumption that the tropical anguillula after its transportation into a temperate zone has adapted itself to the less favorable climatic conditions of the latter in such a manner that the anguillula of the temperate zone favors more the much simpler mode of development which is the more independent of the climate—namely, the direct transformation of the embryo into the filaria-shaped larvæ, which in turn grow directly into parasitic anguillulæ.

According to the statements of various authors Anguillula stercoralis when present in large numbers causes diarrhœa. According to Normand, Grassi, Golgi, Leichtenstern, and others, the worms are found chiefly in the upper parts of the small intestine. According to Leichtenstern and Askanazy the mature animals and the larvæ penetrate not only into the crypts of Lieberkühn, but also into their epithelium and into the connective tissue of the mucosa, and in individual cases may break through the muscularis mucosæ. The mother animals lay their eggs in the intestinal crypts. The embryos when hatched out wander out into the intestine.

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§ 200. **Tricocephalus dispar** (*Trichuris trichuria*), the *whipworm*, is a common and relatively harmless parasite, though according to Askanazy it sucks blood from the intestinal mucosa. It inhabits the cæcum and the neighboring portions of the intestine. It is found also in the domestic animals. The male and female are about 4–5 cm. in length (Fig. 583). The anterior body-half (*a*, *b*) is very thin, thread-like; the posterior which bears the sexual organs (*f*, *g*, *l*, *o*, *p*), is much thicker, in the female (*B*) cylindrical, and in the male (*A*) rolled up and provided with a spiculum (*g*).

FIG. 583.

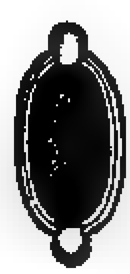

FIG. 584.

FIG. 583.—*Tricocephalus dispar*. (After Küchenmeister and Zürn.) *A*, Male; *B*, caudal end of female; *a*, cephalic end; *b*, anterior portion of body with œsophagus; *c*, stomach; *d*, intestine; *e*, cloaca; *f*, seminal duct; *g*, penis; *l*, bell-shaped penis-sheath, with end of penis; *m*, intestine of the female; *n*, anus; *o*, uterus; *p*, vaginal opening. × 9.

FIG. 584.—Egg of *Tricocephalus dispar*. (After Heller.) × 815.

The eggs (Fig. 584) are an elongated oval, 50 μ long, and possess a thick brown shell, which shows at both poles a peg-shaped, glassy swelling.

The first stage of the development of the embryos takes place in water and in moist earth. It advances slowly, even in summer lasting four to five months, and in the colder months of the year much longer. The eggs are very resistant to cold and drying. (For the literature see *Huber*, "Bibliographie der klin. Helminthologie," München, 1893, p. 213; *Askanazy*, "Der Peitschenwurm," *Deut. Arch. f. klin. Med.*, 57 Bd., 1896; *Heine*, "Anatomie d. Tricocephalus," *Cbl. f. Bakt*, xxviii, 1900).

§ 201. **Trichina spiralis** occurs in two forms—the trichina of the intestine and the trichina of the muscles.

The **intestinal trichina** (Fig. 585) is the sexually mature form, and is a small, white, hair-like worm scarcely visible to the naked eye. The female (*A*) is 3 mm. long, the male (*B*) is much smaller. The posterior part of the body is elongated in both sexes, and in the male (*B*) is provided on the dorsal half with two conical terminal pegs, which are directed toward the belly and are separated from each other by four knob-like papillæ. Instead of a spiculum the muscular cloaca is protruded outward during copulation.

The intestinal canal begins with a muscular mouth, which becoming wider passes into the œsophagus, which throughout its entire length is surrounded by the so-called cell-body—that is, by rows of large cells. The stomach, which follows the œsophagus, is a flask-shaped dilatation of the

intestine, and is lined with finely granular cells. The stomach passes without any essential change of structure into the intestine, which in the male unites with the seminal duct at the posterior end to form the cloaca.

The testicles consist of a pouch, which begins near the caudal end as a blind sac, proceeds as far forward as the cell-bodies, and bending there, passes over into the seminal duct.

The sexual organs of the female (*A*) consist of a single ovary, a uterus and a vagina, which opens externally at the junction of the first and second quarters. The ovary likewise forms a pouch lying close to the posterior end of the body, in which the round eggs develop. The pouch passes anteriorly into the sac-shaped *uterus*.

The eggs develop within the uterus into embryos which are set free at birth.

The **muscle-trichina** (Fig. 586) is a worm 0.7–1 mm. in length, which lives in the muscles of the body. It is usually rolled into a spiral and lies in a capsule, which occasionally contains lime-salts. Between the coils of the worm there is a finely granular mass.

A single capsule may contain three to five trichinæ.

If a piece of muscle containing living trichinæ is taken into the stomach of a host—for example, man—the capsule is dissolved and the trichinæ are set free. In the intestinal canal they attain sexual maturity within two and a half days, when copulation takes place. On the seventh day after the ingestion of muscle trichinæ the birth of embryos begins, which continues some time, even for weeks. A single female trichina may bear from one thousand to thirteen hundred young. According to Pagenstecher, Chatin, Cerfontaine, and Askanazy, the female trichinæ penetrate into the intestinal villi and deposit the embryos in the chyle-vessels, whence their migration begins. To what extent they are swept along passively by the lymph, or to what extent active migration is concerned in their spreading, is a difficult matter to determine. When arriving in the muscles they penetrate the primitive fibres, bring the adjacent contents of the fibre to degeneration, and grow in about fourteen days to fully developed muscle trichinæ. In the neighborhood of the trichinæ there occurs a proliferation of the muscle-nuclei and an inflammation of the connective tissue. At first the muscle-trichinæ are enclosed only by the sarcolemma, which appears thickened and hyaline about them. Later there occurs in the neighborhood an inflammatory proliferation of granulation tissue containing numerous eosinophile cells (Schleip), which leads to the production of connective tissue on the out-

FIG. 585.—Sexually mature trichinæ. *A*, Female; *B*, male. (After Leuckart.) × 120.

side of the sarcolemma and penetrates even within the sarcolemma tube, the muscle-nuclei being destroyed. Fat-cells may appear later in the connective tissue of the capsule, the development of the latter being especially marked at the poles.

The intestinal trichinæ have a limited life of from five to eight weeks. The muscle-trichinæ, on the other hand, may live for a very long, possibly an unlimited time—that is, until the death of the affected individual; or at any rate for years, although, according to Ehrhardt, a few may die before the encapsulation. After some time there frequently occurs a deposition of lime-salts in the capsule, especially at the poles, causing it to appear glistening-white by reflected light, and cloudy and dark by transmitted light. In rare cases the trichinæ after dying also become calcified.

FIG. 566. Encapsulated muscle trichinæ. (After Leuckart.) × 60.

Trichinæ have been observed, besides in man, also in the hog, cat, dog, rat, mouse, marmot, polecat, fox, marten, badger, hedgehog, and raccoon. Through the feeding of trichinous meat muscle-trichinæ may also be developed in rabbits, guinea-pigs, sheep, dogs, etc. Man becomes infected through the eating of uncooked pork. The invasion of the trichinæ produces various phenomena in man. The introduction of trichinous meat into the intestine is followed by the symptoms of an intestinal catarrh. With the invasion of the muscles there are produced pain, swelling, œdema, paralysis, and not infrequently fever. In the blood there occurs a marked increase of the eosinophile cells (Opie, Schleip). The symptoms are most severe in the fourth and fifth weeks. Death not infrequently results. The intensity and severity of the symptoms depend in general upon the number of the worms wandering into the muscles.

The trichinæ are found most abundantly in the diaphragm, tongue, intercostal muscles, the muscles of the neck and larynx, the lumbar muscles, and are scattered most sparsely in the distant muscles of the extremities. They are usually most numerous about the insertions of the tendons.

According to *Frothingham* (*Jour. of Med. Res.*, 1906), the trichina embryos are found in the sinuses of the mesenteric lymph-nodes and in the liver sinusoids, showing that they enter the lymph-stream and are distributed by the circulating blood. Trichina embryos are found in the areas of hæmorrhage occurring in the lungs. Local destruction of tissue may take place in the liver, pancreas, brain, and heart as a result of the parasite leaving the blood-vessel. The capsule of the encysted trichinæ is formed of connective tissue which surrounds the whole of the invaded fibre.

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§ 202. **Filaria or Dracunculus medinensis**, the Guinea-worm (Fig. 587), is a thin, thread-like female worm from 60 to 100 cm. in length. The males (observed by Charles) which were attached to female filariæ, were only 4 cm. long. The anterior extremity is rounded off, while the posterior tapers into a pointed tail which is curved toward the belly. The external covering consists of a firm cuticle, which at the cephalic end is thickened in the form of a shield. The intestinal canal is narrow and has no anus. The uterus, filled with young, takes up nearly the whole of the body-cavity. The embryos, which are set free by the bursting of the mother-worm, have a firm cuticle and an awl-shaped tail. As intermediate host, the embryos seek out small crustaceæ, in which they are probably taken into the stomach of man with the drinking-water. In Africa and Asia the worm is of frequent occurrence. It develops in the skin to sexual maturity and causes abscesses of the affected region. It is usually found on the lower extremities, especially in the region of the heels.

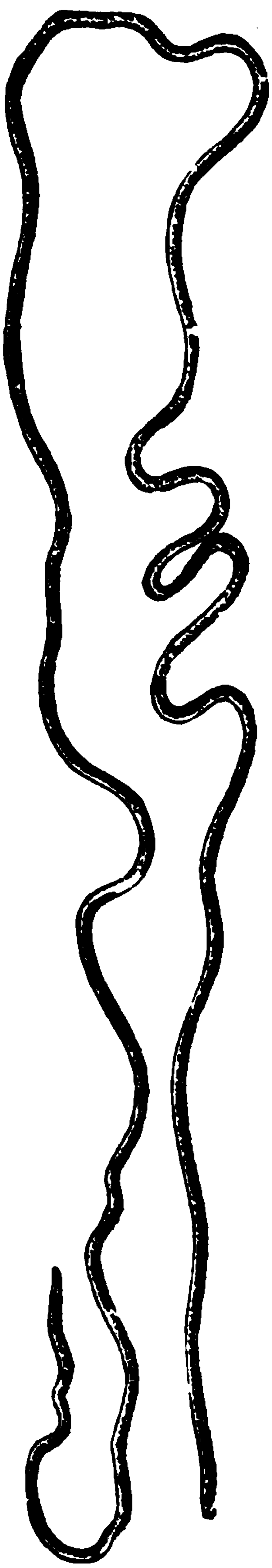

FIG. 587.

FIG. 588.

FIG. 587.—*Filaria sive Dracunculus medinensis.* (After Leuckart.) Natural size.

FIG. 588.—Embryo of *Filaria Bancrofti*, known as *Filaria sanguinis hominis.* (After Lewis.) × 400.

Filaria sanguinis hominis is the name given to the *larvæ* (Fig. 588) of a worm, which occur in the blood and lymph of man.

and are about 0.35 mm. in length. The sexually mature worm is filiform, the male about 8 cm. long and the female 15 cm. It is called **Filaria Bancrofti** after its discoverer. The worm inhabits the lymph-vessels, particularly those of the scrotum and lower extremities, and may be present in large numbers. It causes lymph-stasis and inflammations which lead to *swellings of the lymph-glands* and to *elephantiasis-like thickening of the tissue*, associated with œdema and lymphangiectasis. Purulent inflammations, lymph-abscesses, buboes, chylous hydrocele, and chylous ascites may appear in consequence of its presence.

From the lymphatics of the limbs and scrotum the eggs and embryos (0.35 mm. long) (Fig. 588) pass into parts of the lymphatic system and into the blood, giving rise to hæmaturia, chyluria, and chylous diarrhœa. According to Manson and Scheube the filariæ are present in the blood taken from the skin only during the night; von Linstow explains this phenomenon as due to the fact that during sleep the peripheral vessels become dilated, and so permit the entrance of the filariæ, while the capillaries, being narrower during the day, do not permit such entrance. The hæmaturia is the result of the collection of embryos in the blood-vessels of the urinary tract. The chyluria and the chylous diarrhœa, on the other hand, are due to the obstruction by the parasites of the thoracic duct, thus causing a lymph-stasis which extends to the lymphatics of the bladder and intestine and there occasions the escape of lymph. According to Scheube the rupture of the lymphatics is also attended by a rupture of blood-vessels, so that blood becomes mixed with the lymph. The embryos may pass out from the urinary apparatus through the urine.

The distribution of the embryos is, according to Manson, accomplished by means of mosquitos, which take up the parasite during the act of blood-sucking. In the mosquitos they pass through a second stage of development and are then (James) after two or three weeks ready for the infection of a new host. Manson formerly held the opinion that they entered the water, and in a free condition were taken up in the water into the intestinal tract. The investigations of James, Low, Grassi, and Noè, who followed their development and migration in the body of mosquitos, make it seem probable that they are transmitted to a new host through the bite of the mosquito.

The Filaria sanguinis occurs, so far as is known, only in the tropics (Brazil, Egypt, Algiers, Madagascar, Zanzibar, Soudan, South China, Calcutta, Bahia, Guadeloupe).

Of the **Acanthocephala**, nematode-like worms having no intestine, and possessing at the anterior end a retractile proboscis set with hooklets, the most important is the *Echinorhyncus gigas*. The male is 10–15 cm. long, and the female 30–50. It occurs chiefly in the intestine of the pig, and penetrates into the intestinal wall. According to Lindemann, it occurs in Southern Russia also in man. The rose chafer and the May beetle serve as intermediate hosts.

The *Filaria bancrofti* is found in the West Indies and occasionally in the Southern States. More rarely cases are found farther north.

Mackenzie estimated the number of filaria-embryos present in the total bulk of the blood of a case of hæmatochyluria closely studied by him at from thirty-six to forty millions. The patient died from empyema; during the disease the filariæ died.

In the **domestic animals** numerous *filaria-species* occur and inhabit different parts of the body. *Filaria papillosa* is a common parasite of the horse, donkey, and cattle; it lives in the serous cavities and reaches a length of from 5–18 cm. *Filaria hæmatica*, a worm 13–13 cm. long, inhabits the right heart and the pulmonary artery of the dog, and in this situation gives off its embryos to the blood-stream. It occurs particularly

in America, China, and India. *Filaria hæmorrhagica* or *multipapillosa* causes a nodular cutaneous affection in the horse and donkey.

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III. Arthropoda.

1. *Arachnida.*

§ 203. The parasites included among the **Arachnida** are chiefly epizoa, which either temporarily or permanently inhabit the skin. Only one species—*Pentastoma*—occurs in the larval form within the tissues. The most common parasites of this group belong to the *Mites* (*Acarina*). The pentastoma belongs to the family of *tongue-worms* (*Pentastomidæ* or *Linguatulidæ*).

(1) **Acarus scabiei** or **Sarcoptes hominis**, the **itch-mite**, is a parasitic mite the size of a pinhead with a turtle-shaped body, provided on the ventral surface both anteriorly and posteriorly with two pairs of legs, each of which is furnished with bristles (Fig. 589). The anterior pairs of legs extend out into pedicled clinging-discs. The same arrangement is found in the posterior two pairs in the male, while in the female both of the posterior pairs end in long bristles. Several bristles are also found

along the border of the posterior portion of the body, while the back is studded with tooth-like knobs. The head is round and likewise set with bristles. The female is nearly double the size of the male.

FIG. 589.—Female itch-mite, ventral surface. × 40.

The mite lives in the epidermis (Fig. 590, *a*, *d*) in which it forms burrows, some of which are 10 cm. long.

In the burrows the female (*d*) lays the eggs, which develop *in situ* into the young itch-mites (*e*), which penetrate still deeper into the epidermis, and after repeated sheddings of their skins grow into sexually mature animals. The skin responds to the irritation produced by the

FIG. 590.—Scabies (alcohol, carmine). *a*, Horny layer of the epidermis, perforated by numerous burrows of the itch-mite; *b*, mucous layer, and papillary body, the latter greatly enlarged and infiltrated with cells; *c*, cutis infiltrated with cells; *d*, section through a fully developed itch-mite; *e*, eggs and embryos of different sizes; *f*, fæces. × 20.

presence of the mites by an increased production of epithelial cells (*a*) and inflammation (*c*). The latter is still further increased through the scratching of the spots which itch in consequence of the invasion.

2. **Leptus autumnalis,** the *harvest-mite* (Fig. 591) is the red-colored larva of a variety of *Trombididæ*, which lives upon grasses and bushes and upon grain, and when occasion offers alights upon the skin of man, where it penetrates the epithelium and causes itching and inflammation.

3. **Demodex** or **Acarus folliculorum hominis** (Fig. 592) occurs either singly or in numbers in the hair-follicles of the face, as well as in the ducts of the sebaceous and Meibomian glands. Hausche found the demodex on the eyelashes in seventy-nine per cent., and Joers in sixty-four per cent. of the cases examined. Children under one year of age were free. The female is 0.4 mm. long, the male 0.3 mm. The eggs are deposited upon the shaft of the hair or upon any other portion of tissue, and develop after two sheddings into sexually mature animals which are found in the entrances to the hair-follicles and sebaceous glands, with their heads directed inward. The assumption that the demodex causes inflammation (acne, blepharitis acarica) is not supported (Joers, Hausche), since in spite of its presence in the great majority of cases signs of inflammation are wanting.

It has on its anterior ventral surface (Fig. 592) four pairs of short thick feet. The head possesses a snout and two feelers.

4. **Ixodes ricinus,** the *wood-jack* or *wood-tick* (Fig. 593), is a fairly large yellowish-brown member of the Arachnida belonging to the ticks.

FIG. 593.

FIG. 591. FIG. 592. FIG. 594.

FIG. 591.—*Leptus autumnalis.* (After Küchenmeister and Zürn.)

FIG. 592.—*Acarus folliculorum hominis.* (After Perls.) × 300.

FIG. 593.—*Ixodes ricinus*, sucked half full of blood. × 2.

FIG. 594.—Cephalic end of *Pentastoma denticulatum.* (After Perls.) × 40.

It has a black head provided with a sucking apparatus, and a very distensible leathery body. It is of common occurrence upon grass and bushes, and sometimes alights upon man or beast. By means of its sucking apparatus it draws blood from the skin and swells up to a very remarkable extent.

5. **Pentastoma denticulatum** is the larva of **Pentastoma tænoides**, a lancet-shaped animal belonging to the tongue-worms or *Pentastomidæ*. It inhabits the nasal, frontal, and maxillary cavities of various animals, especially of the dog, very rarely of man (Laudon) and occasions inflammations. The female of the mature animal is 50–80 mm. long, and anteriorly from 8–10 mm. broad; the male is 16–22 mm. long, and anteriorly from 3–4 mm. broad. The body consists of eighty-seven to ninety segments, the most anterior of which bear lateral segment-appendages, the pairs of limbs. The eggs, which are produced in very great numbers, are oval. The larva is 4–5 mm. long, 1.5 mm. broad, plump, flattened, and inhabits chiefly the liver, lung, or spleen, or more rarely the other organs of man and the herbivora. It occurs in the form of a small nodule encapsulated in connective tissue. The body consists of about fifty ring-shaped segments which are provided at the borders with spines (Fig. 594), and the cephalic end is provided with four hook-shaped feet. The eggs are taken in from the external world through the intestinal tract. The parasites set free in the intestine wander by means of a boring apparatus through the mesentery into the mesenteric lymph-glands, or penetrate directly into the blood-vessels, and are carried by the blood-stream to the liver or even to the lungs, where after shedding they develop into the encysted larvæ. The larvæ may in their wanderings gain access to the nasal cavity of their host, and develop into mature animals, although the further development usually takes place only after their reception into a new host.

According to the published reports of *Tanaka* a small red mite occurs in great numbers in different parts of Japan during midsummer, and clinging firmly to the skin of man causes the so-called *Kedani-disease*, which is characterized by inflammation of the skin and lymph-glands, with high fever, and often ends fatally. It is probable that these symptoms are due to secondary infections (proteus and streptococci) in the bites of the mite. *Argas reflexus*, a tick, causes by its bite not only local inflammation, but also nausea, diarrhœa, cardiac palpitation, asthma, etc., through a poison derived from its salivary glands. It is found also in pigeons.

In the **domestic animals** living **mites** occur very frequently as parasites of the skin, and represent different species of various families (*Sarcoptides, Dermatocoptes, Dermatophages*, and *Acarides*).

Sarcoptes hominis, the *burrow-mite* or *itch-mite* of man, is found also in horses and Neapolitan sheep. In addition still other different species of sarcoptes may be distinguished as parasites of the domestic animals—for example, *Sarcoptes squamiferus* in dogs, hogs, sheep and goats, and *Sarcoptes minor* in cats and rabbits.

Dermatophagus, the *devouring-mite* (Fig. 595), with a broad head, occurs in different animals, and different species may be accordingly distinguished. It lives upon the cells of the epidermis and causes a desquamation of the skin.

Dermatocoptes, the *sucking-mite* (Fig. 596), with long narrow head, takes blood and lymph from the skin and causes inflammation. *Dermatocoptes communis* occurs in horses, cattle, and sheep.

Dermatocoptes cuniculi is a parasite of the rabbit's ear, and causes the ear-scab which usually appears on the inner side of the auricle.

Symbiotes equi of *Gerlach* is a mite which occurs chiefly upon the feet of the heavy English and Scotch horses, and causes a moist dermatitis, often incorrectly called *malanders*.

Dermanyssus avium is a long, red, blood-sucking mite, about 1 mm. long, and is often found upon birds.

Dermatoryctes mutans causes the foot-itch of chickens whereby the skin acquires a mortar-like scabby covering.

[illegible] the mite of the hair-follicles [illegible] in the dog [illegible] in the hog, cattle, and the goat [illegible] causes the formation of scales, falling out of the hair, and a pustular eruption.

[illegible] inflammations and ulcers particularly [illegible] and the outer surface of the thighs. The [illegible] in great numbers [illegible]. The mite may develop also on [illegible]

Fig. [illegible]. Fig. [illegible].

Fig. [illegible]. — Male of [illegible], seen from the ventral side. (After Fürst.) [illegible]

Fig. [illegible]. — Male of [illegible], seen from the ventral side. (After Fürst.) [illegible]

[illegible] occur in dogs, cattle, and sheep [illegible] occur in pigeons and other birds [illegible] occur in the domestic animals [illegible] occurs also in dogs and chickens.

[illegible] occur also in cattle, sheep, and goats, and in certain regions are [illegible] common in the first-named.

[illegible] *Insecta.*

§ 264. The parasites belonging to the class of *Insecta* are for the greater part epizoa. In part they are but transient inhabitants of the skin, deriving from it their nourishment; in part they are permanent inhabitants and utilize the skin structures for the deposit of their eggs. Of the numerous species belonging to this class the following may be mentioned:

1. **Pediculus capitis**, the *head-louse* (Fig. 397), inhabits the hairy portions of the head, and derives its nourishment (i.e., blood) from the skin by means of its feeding apparatus. Its eggs (nits) are barrel-shaped and white, and are attached to the hairs by means of a chitinous sheath. The embryo hatches in about eight days. In consequence of the scratching induced by the itching there often arise inflammations of the skin, in particular eczemas, which are often sufficiently severe.

2. **Pediculus pubis** (*Phthirius inguinalis*), the *pubic* or *crab-louse* (Fig. 398), inhabits the hairy parts of the trunk and extremities. Its habits of life are the same as those of *Pediculus capitis*.

3. **Pediculus vestimentorum**, the *clothing* or *body-louse* (Fig. 399), lives in the wearing apparel, and lays its eggs in the same. It gets upon man to obtain its nourishment.

(4) **Cimex lectularius,** the bedbug, dwells in beds, floors, closets, etc. During the night it gets upon man to suck blood. It causes wheals in the skin.

(5) **Pulex irritans,** the *common flea,* also draws blood from the skin. At the point where it has sucked there is found a little punctate hæmor-

FIG. 597. FIG. 598. FIG. 599.

FIG. 597.—Female of *Pediculus capitis*, seen from the ventral surface. (Küchenmeister and Zürn.) × 13.

FIG. 598.—Male of *Pediculus pubis*, seen from the ventral surface. (Küchenmeister and Zürn.) × 13.

FIG. 599.—Female of *Pediculus vestimentorum*, seen from the ventral surface. (Küchenmeister and Zürn.) × 9.

rhage. Occasionally it causes wheals and swellings. It lays its eggs in the cracks of floors, in sawdust, etc.

(6) **Pulex penetrans** (*Sarcopsylla penetrans*), the *sand flea,* occurs in South Africa in the sand. The female lays her eggs in the skin, thereby causing an intense inflammation.

(7) **Mosquitos** provided with stinging and sucking apparatus (*Culicidæ* and *Tipulidæ*), **horse-flies** (*Tabanidæ*), and **flies** (*Stomoxyidæ*) draw blood frequently from the skin of man. Various **flies** (*Œstridæ*, biting

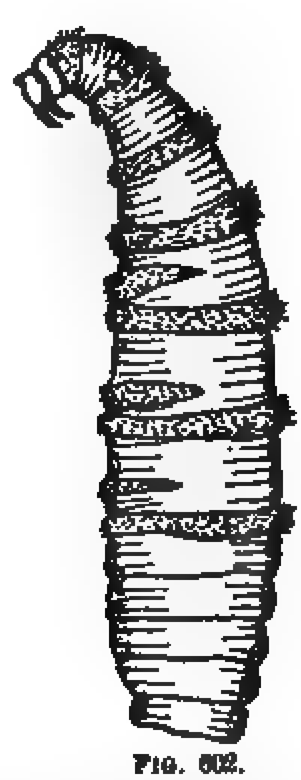

FIG. 600. FIG. 601. FIG. 602. FIG. 603.

FIG. 600.—Larva of *Anthomia canicularis.* (After Braun.) About × 6.
FIG. 601.—Larva of *Musca vomitoria.* (After Braun.) About × 6.
FIG. 602.—Larva of *Lucilia macellaria.* (After Braun.) About × 6.
FIG. 603.—Larva of *Dermatobia cyaniventris.* (After Blanchard.) About × 6.

bot-flies, *Muscidæ* or *blow-flies*) occasionally lay their eggs in the skin, in ulcers or wounds, or in the accessible body-cavities, in consequence of which the maggots developing cause local destruction of tissue and inflammation (*myiasis*). Under certain conditions their larvæ (for example, that of *Anthomia canicularis*, Fig. 600) may get into the intestinal tract with the food and there undergo further development (*myiasis intestinalis*). This is especially likely to occur when abnormal conditions which interfere with digestion are present in the stomach and intestine. The *eggs of the Muscidæ* (in Europe usually of *Sarcophila wohlfarti* and *Musca vomitoria* [Fig. 601], in America of *Compsomyia* or *Lucilia macellaria* [Fig. 602], and *Musca anthropophaga*), when laid upon the mucous membranes or in wounds, hatch after a few hours, and cause destruction of the neighboring soft parts through their efforts to obtain nourishment. In the auditory canal, nose, and antrum of Highmore the bones may be laid bare (*myiasis mucosa*). In the course of about a week the larvæ leave the ulcers and pass into the pupa stage in the earth. The *Œstridæ* (in Europe, *Hypoderma bovis* and *Hypoderma diana*; in America, *Dermatobia cyaniventris* [Fig. 603] or *Cuterebra noxialis*) lay their eggs upon wounds or in the intact skin. The larvæ, hatching very soon, penetrate into the cutis by means of their hooklets, and after several sheddings grow in from one to six months into larger larvæ about 2 cm. long. They cause, particularly in their later stages, painful swellings of the neighboring tissue (*myiasis œstrosa*).

FIG. 604. *Gastrophilus equi.* (After Brauer.) *a*, Male; *b*, larva.

Parasites belonging to the *Muscidæ* and *Œstridæ* play a more important rôle in the case of the **domestic animals** than in man; and the larvæ of the species of *Œstrus* in particular occur as parasites in animals. For example, the larvæ of *Gastrophilus equi* (Fig. 604), *Gast. pecorum* and *Gast. hæmorrhoidalis* inhabit the stomach and adjacent portions of the intestinal tract of the horse, where they complete their development up to the pupa-stage, when they leave the animal.

Œstrus ovis lays its larvæ in the nasal cavities of sheep, whence they may wander, under certain conditions, into the frontal, nasal, and maxillary cavities, or even into the cranial cavity, and excite inflammation.

Hypoderma or *Œstrus bovis*, the biting fly, or bot-fly, lays its eggs upon the skin of cattle. The larva bores into the skin and enters the spinal canal of cattle, completing here its development up to the pupa-stage, at which time it leaves the animal. According to *Schneidemühl*, the larvæ do not always enter through the skin, but are more often taken in with the food, whereupon they penetrate through the wall of the œsophagus toward the skin and spinal canal. The latter follows from the fact that they are found in the wall of the œsophagus from October to January, and under the skin, on the other hand, from January to April. In the skin they cause the so-called "fly-boils."

Sarcophila wohlfarti (*Sarcophaga magnifica*) lays its larvæ upon the skin of horses, sheep, cattle, dogs, and geese. *Lucilia macellaria* lays its eggs between the hind legs of lambs suffering with diarrhœa. The larvæ seek the thick-wooled portions of the root of the tail and the lumbar region and bore into the skin.

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GENERAL INDEX.